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**From the Department of Public Health and Clinical Medicine**  
**Occupational and Environmental Medicine**

**Mortality and Morbidity in Lead Smelter Workers with Concomitant**  
**Exposure to Arsenic**

**By**

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## **ABSTRACT**

Arsenic is a well-known lung carcinogen in humans. In 2006, IARC upgraded inorganic lead as a possible human carcinogen (2A). The aim of this thesis has been to evaluate the lung cancer mortality and incidence in long-term exposed primary lead smelter workers and also to estimate present exposures to arsenic and lead in relation to those occurring in the past. The basic cohort (N=3832 workers; hired before 1967 and followed up from 1950-1981; SMR comparisons with general and local reference populations) showed an excess of deaths for total mortality, malignant neoplasms (e.g. lung and stomach cancer), ischaemic heart diseases, and cerebrovascular diseases compared to the general population. In a subcohort of lead workers (N=437; regular blood lead sampling since 1950) only the raised SMR for lung cancer (162) was sustained. In a follow-up study of the basic cohort (N=3979), a subcohort of lead exposed workers (N=1992) was formed. The expected mortality in 1955-1987 and cancer incidence in 1958-1987 were calculated relative to county rates. A cumulative blood lead index (CBLI) was used for dose-response analyses. The lung cancer incidence was raised in the total cohort (SIR 2.8; 95 % CI 2.1-3.8). A higher lung cancer risk was observed in workers hired before 1950 (SIR 3.6; 95 % CI 2.6-5.0). The increased lung cancer risks were further elevated in the subcohort of lead exposed workers, especially in the highest exposed subgroup (SIR 5.1; 95 % 2.0-10.5; latency period of 15 y). No excesses of other malignancies were observed. The increased relative risks for lung cancer may have been caused by interactions between inorganic lead and other substances at the smelter, e.g. arsenic. To further analyze the effects from inorganic lead, two subcohorts of workers at the lead departments were formed from the original cohort (N=3979), one of 710 workers and the other of 383 workers. The lung cancer incidence was raised in both subcohorts (Lead subcohort 1; SIR 2.4; 95 % CI 1.2-4.5; Lead subcohort 2; SIR 3.6; 95 % CI 1.2-8.3). Among the 10 workers that had developed lung cancer in lead subcohort 1 all but one had a considerable exposure also to arsenic. Thus, a possible interaction effect between lead and arsenic may explain the increased lung cancer risks. To further elucidate the impact from lead and arsenic a case-control study was undertaken. In the basic cohort (N=3979), 46 male workers had contracted respiratory malignancies. They were compared with 141 age-matched male referents from the primary smelter by conditional logistic regression analysis using smoking habits, cumulative blood lead and air arsenic exposure as predictor variables. The lung cancer cases showed a significantly higher smoking rate than referents (Odds ratio, OR = 4.0; 95 %

CI 1.6-10.1;  $p=0.003$ ). When restricted to smokers, the cumulative arsenic air exposure index, but not the lead exposure indices, were significantly higher among the cases (OR=1.07; 95 % CI 1.02-1.11;  $p = 0.005$ ).

Accordingly, cumulative arsenic exposure and smoking were identified as significant risk factors for the development of lung cancer in the final analyses, while lead exposure was not a significant risk factor. However, inorganic lead still may play a minor role in the multifactorial genesis of lung cancer.

These studies describe risks from exposures occurring from time periods before 1950 up to 1981. Because of the long latency period for lung cancer, exposures after 1970 probably have had limited impact on the reported results. Compared to the levels in the early 1970's present exposures to arsenic are lower by a factor of ten or more and risks probably correspondingly lower.

## LIST OF PUBLICATIONS

This thesis is based on the following published original articles, which will be referred to in the text by their Roman numerals.

- I Gerhardsson L, Lundström N-G, Nordberg GF, Wall S. Mortality and lead exposure – a retrospective cohort study of Swedish smelter workers. *Brit J Ind Med* 1986; 43: 707-712.
- II Lundström N-G, Nordberg G, Englyst V, Gerhardsson L, Hagmar L, Jin T, Rylander L, Wall S. Cumulative lead exposure – relationship to mortality and lung cancer morbidity in a cohort of smelter workers. *Scand J Work Environ Health* 1997; 23: 24-30.
- III Englyst V, Lundström N-G, Gerhardsson L, Rylander L, Nordberg G. Lung cancer risks among lead smelter workers also exposed to arsenic. *Sci Total Environ* 2001; 273: 77-82.
- IV Lundström N-G, Englyst V, Gerhardsson L, Jin T, Nordberg G. Lung cancer development in primary smelter workers: a nested case-referent study. *J Occup Environ Med* 2006; 48: 376-380.

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## Abbreviations

ACGIH	American conference of governmental industrial hygienists
B-Pb	Blood lead level
BAT	Best Available Techniques
BEI	Biological Exposure Index
BPbY	Number of years when blood lead samples were obtained
CAA EI	Cumulative air arsenic exposure index
CBLI	Cumulative blood lead index
CI	Confidence Interval
IARC	International Agency for Research on Cancer
LOAEL	Lowest Observed Adverse Effect Level
MAK	Maximale Arbeitsplatz Konzentration
OEL	Occupational Exposure Limit
OR	Odds Ratio
PBPb	Peak blood lead concentrations
SCOEL	Scientific Committee on Occupational Exposure Limits
SIR	Standardized Incidence Ratio
SMR	Standardized Mortality Ratio
TLV	Threshold limit value
TWA	Time weighted average



## 1. INTRODUCTION

### ***1.1 Occurrence, use, exposure to inorganic lead***

Lead is one of the oldest metals known to man. It was mined in Spain already in 2000 B.C. In the general environment, there is oral exposure through food and water. Additional exposure may originate through contamination from soldered tin cans, lead-glazed or lead-painted pottery or crystal glass. In some areas, there may be considerable exposure through plumbosolvent drinking water by contamination from lead pipes (Mushak et al. 1989). Children and adults may get additional exposure through intake of lead-containing paint flakes in some countries. Small children are at particular risk due to repeated hand to mouth activities. There may also be exposure from cigarettes and tobacco, which contain inorganic lead as well as from alcoholic beverages, e.g. wine and “moonshine whiskey”. Humans are exposed to inorganic lead in a multitude of occupational settings, e.g. lead smelters, metals scrapping, spray painting and storage battery manufacturing (Skerfving and Bergdahl 2007).

In many countries, the exposure has decreased dramatically since the 1980's, mainly because of the gradual and increasing use of unleaded gasoline. In several regions, however, lead exposure is still a considerable public health problem in the general population, particularly among pregnant women and infants who have the highest risk of developing adverse health effects (Mushak et al. 1989).

The softness and the low melting point of the metal are advantageous and makes it very easy to handle and fashion. It has a high resistance to corrosion, which makes it very suitable for weatherproofing buildings and for equipment used in the manufacture of acids. The high density of lead makes it particularly appropriate as a shield against radiation in the nuclear industry and against x-rays in hospitals. For the same reason lead is also good at stopping sound waves. Thus, it may be used to reduce noise from machinery in factories and from engine rooms on ships. The most important use of lead today, however, is in lead-acid storage batteries, which provides power in numerous situations. Other important uses include paint pigments, glass, plastics, and ceramics. It is also used in ammunition, cable-covering materials, casting metals, solders, pipes, traps and bends. Smelting and refining operations, scrap recovery, automobile radiator repair, construction

and demolition processes, and firing range operations may result in significant lead exposure of workers (Skerfving and Bergdahl 2007).

About 3 million tonnes of lead are mined in the world each year. Lead mining is found all over the world but the largest mining countries are Australia, China and the US. These three countries account for more than 50% of the primary production. A further 3 million tonnes of lead are produced from secondary sources each year, by recycling scrap lead products such as sheet, pipe and batteries (Lead Development Association 2007). Today, more lead is produced by recycling than by mining in the western world. More than 50% of the lead consumed in the US is in the form of batteries. Of this, about 90% is reclaimed. At present, battery scrap is converted to impure lead or lead alloys by pyrometallurgical processes employing blast, reverberatory, or rotary furnaces. The overall recovery of the metallic components of scrap in plants having both reverberatory and blast furnaces is exceeding 95%.

## **1.2 Metabolism of lead in man and animals**

### **1.2.1 Absorption**

#### **1.2.1.1 Inhalation**

The exposure through ambient air is low in most areas with average levels around or lower than  $0.1 \mu\text{g}/\text{m}^3$  (Vahter and Slorach 1991). These levels correspond to an inhaled amount of less than 1-2  $\mu\text{g}/\text{day}$ . Considerably higher levels up to about  $10 \mu\text{g}/\text{m}^3$  have been reported from some areas. The particle size distribution may vary considerably between different areas and is important for the deposition in the airways. Inorganic lead may also be inhaled through cigarette smoking. The estimated lead content in a cigarette is about 3-12  $\mu\text{g}$ , of which about 2% is inhaled by the active smoker (Skerfving 1993). Children and adults may also be exposed through passive smoking.

Some hobbies may be connected to lead exposure, e.g. indoor shooting (Svensson et al. 1992), tin soldier moulding, ceramics work using lead-containing glazes and motor sports involving work with exhaust systems.

Also jogging or cycling in contaminated areas may increase the inhalational exposure.

Particles with an aerodynamic diameter above 5  $\mu\text{m}$  are mainly deposited in the upper airways, cleared by the mucociliary mechanism, and swallowed (Skerfving 1993). A part of this lead is then taken up by the gastrointestinal tract. For particles inhaled via the mouth, and with a size of 0.05  $\mu\text{m}$  and a respiratory rate of 15/min, about 40% of the inhaled lead is deposited in the airways (Chamberlain 1985). For smaller particles, the deposited fractions are lower. Most of the lead deposited in the alveolar part of the lung is absorbed. The rate of absorption is dependent upon solubility of the chemical species of lead. In human radiotracer experiments, the absorption has usually been completed within 24 hours (Morrow et al. 1980; Chamberlain 1985). The percentage of particles less than 0.5  $\mu\text{m}$  retained in the lung increases with reduction in particle size.

### **1.2.1.2 Ingestion**

Soil, street and home dust may contain increased lead levels. Children may have an additional exposure through repeated hand-to-mouth activities (Thornton et al. 1990) or through the pica behavior. The peak intake in children is when they are about two years old. The intake is higher during the summer period.

In radiotracer experiments in fasting subjects, the absorption was 37-70 % (average about 60%; Skerfving 1993). Of soluble lead salts, the reported uptake with meals has been 4-21% (average about 8%; Skerfving 1993). The uptake of inorganic lead in adults usually ranges between 10-20%. Children seem to have a higher uptake than adults (Ziegler et al. 1978). In adults, there seems to be a considerable inter-individual variation in lead uptake from the gut (Blake 1976). In rats, very large doses were absorbed less efficiently than small ones (Aungst et al. 1981). In humans there was no effect of moderate lead doses on the fractional uptake of lead (Chamberlain 1985).

### 1.2.1.3 Skin

The uptake of inorganic lead salt applied on the skin is limited. In one study the uptake was less than 0.1% in one month (Moore et al. 1980).

## 1.2.2 Distribution

Lead is absorbed to the blood plasma, and then rapidly equilibrates between plasma and the extracellular fluid. More slowly, but within minutes, lead is transferred from plasma to blood cells. The turnover of lead in plasma is very rapid. The half-life after intravenous injections in humans was about one minute (Campbell et al. 1984). Within the blood, about 99% of the Pb content is in the red cells and mostly less than 1% in plasma (Ong et al. 1990). In red blood cells, most of the inorganic lead is bound to  $\delta$ -aminolevulinic acid (ALAD; Bergdahl et al. 1997) but also to e.g. hemoglobin and to the erythrocyte membrane. The binding of lead in red blood cells may vary between different species. This variation may affect the relationship between B-Pb on the one hand and exposure, organ concentrations, and effects on the other. The lead fraction in plasma rises with increasing blood lead concentrations (DeSilva 1981).

Among the soft tissues, lead is distributed to the bone marrow, the liver and the kidney (Barry 1975; Skerfving et al. 1993). Lead does, to some extent, pass the blood-brain barrier into the nervous system. Such passage is probably higher in infants than in adults according to animal experiments (Mahaffey 1983). The distribution in the central nervous system is uneven with higher levels in e.g. hippocampus and the amygdala. The lead concentration in the cerebrospinal fluid is very low. It seems to be positively correlated with the plasma lead concentration but not with B-Pb.

In animal experiments (Aungst et al. 1981) there is no constant relationship between lead levels in blood and in soft tissues. The accumulation in liver and kidney seems to be higher than in blood, while it is lower in the central nervous system. The peripheral nervous system may accumulate considerably more lead than the CNS.

Lead is also distributed to the gonads (US EPA 1986) and accumulates in the male reproductive tract (Johansson and Wide 1986). Inorganic lead is

also incorporated in the seminal fluid and transferred into the fetus and milk (Skerfving 1993).

A large proportion of the absorbed lead is transferred into the skeleton, harboring about 90% of the body burden (Barry, 1975). In lead workers this fraction may be even higher. There are at least two pools of lead in the skeleton. One is found in trabecular, spongy bone (Schütz et al. 1987a) and the other in cortical, compact bone (Christoffersson et al. 1984; Somerville et al. 1989; Gerhardsson et al. 1993). The skeleton contains about 20% trabecular and about 80% cortical bone. The turnover rate of lead in the skeleton is probably higher in infants than in adults (Chamberlain 1985).

The lead content in the skeleton in occupationally unexposed subjects varies in different geographical areas of the world. It is around a few milligrams in prehistoric subjects, living in a world with no traffic or industries (Ericson et al. 1979), about 10 mg in temporary Scandinavians (Schütz et al. 1987a) and about 100 mg in subjects from the UK (Barry 1975) and the US (Ericson et al. 1979). In long-term and heavily exposed lead smelter workers the skeletal lead content may be in the order of 1 g. There is a continuous turn-over of the skeleton. In long-term exposed subjects, the skeletal pool works as an endogenous source of lead.

### **1.2.3 Elimination**

Lead is filtered through the glomeruli of the kidneys, followed by partial tubular reabsorption. There is a circadian rhythm in urinary lead excretion, both in unexposed subjects and exposed workers (Aono and Araki 1988), with a decrease during the night. The excretion rate is also affected by the urinary flow.

There is a non-linear relationship between lead concentrations in urine and B-Pb. On the other hand, the relationship between urinary-Pb and plasma-Pb seems to be linear. There may be considerable inter-individual variation in the urinary lead excretion at a certain blood lead level (Skerfving et al. 1985).

Lead is also excreted in bile and pancreatic juice, and is eliminated through feces (Skerfving 1993). At low exposures, the excretion in the feces is about half that in the urine, at higher levels probably relatively smaller. A very

small fraction is excreted in sweat, seminal fluid, hair and nails (Skerfving and Bergdahl 2007).

A correlation has been reported between lead levels in maternal blood and in placenta (Schramel et al 1988). The levels in placenta were higher in occupationally lead-exposed women than in non-exposed ones. There is a transplacental passage of lead to the fetus, both in animal experiments and in man (Mayer-Popken et al. 1986). In animal experiments, the growing organism accumulated more lead in the CNS than does the adult animal (Momcilovic and Kostial 1974). The blood-lead levels in the child at birth are associated with that in the mother. The concentration in the child seems to be somewhat lower than in the mother, in whole blood as well as in red blood cells and plasma (Cavalleri et al. 1978). There is usually a decrease of B-Pb in the beginning of pregnancy. This is probably mainly due to an expansion of the plasma volume.

Lead is excreted in milk, probably mainly bound to casein (Beach and Henning 1988). In cows (Oskarsson et al. 1992) and rats (Palminger and Oskarsson 1991) there is an exponential increase of lead levels in milk with increasing B-Pb. In the rat (Palminger and Oskarsson 1991) and mouse (Keller and Doherty 1980), there is a linear relationship between lead levels in plasma and milk. In the rat, the ratio of lead in milk and plasma is about 8 (Palminger and Oskarsson 1991), in the mouse about 25 (Keller and Doherty 1980). Low levels are found in human milk, generally in the order of 10 nmol/L (Schramel et al. 1988), possibly higher in colostrums than in mature milk (Sternowsky and Wesslowski 1985). The concentration in milk is associated with, but considerably lower than the woman's whole blood concentration. On the other hand, the levels in milk are higher than in plasma. The levels of lead in breast milk from occupationally unexposed females do not differ from levels in milk formulas (Skerfving 1993).

#### **1.2.4 Lead compartment model**

A metabolic model of lead may be based on several body pools. A five-compartment model has been suggested by Skerfving et al. (1993) comprising plasma, blood cells, soft tissues, trabecular bone and cortical bone. The half-life in blood and the soft tissue compartment is about 3-4 weeks (Rabinowitz et al. 1976; Schütz et al. 1987b). The half-life in some trabecular bones, e.g. vertebrae is about 1-2 years (Schütz et al. 1987a).

Considerably longer biological half-times have been reported from studies in cortical bone, 5-10 years (Nilsson et al. 1991; Börjesson et al. 1997). The data on the elimination of lead from blood during a long time period after the cessation of exposure indicate an inter-individual variation in skeletal lead kinetics (Schütz et al. 1987b). Indications of such a difference have also been reported in dogs (Fisher 1969). The inter-individual variation in kinetics of lead metabolism, in e.g. soft tissues and in bone, may lead to different risks of adverse effects in exposed subjects (Skerfving 1993).

Age is an important determinant of lead metabolism (US EPA 1986) with a higher absorption from the GI-tract in infants than in adults. Simultaneous intake of lead, calcium and/or phosphate may reduce the GI-absorption of lead (Heard and Chamberlain 1984, James et al 1985). Milk is a major source of both calcium and phosphorous. However, milk seems to contain several components that seem to counteract the expected effects from calcium and phosphate, leading to an increased instead of decreased lead uptake. It is not known which factor may be responsible for the increased lead uptake.

Phytic acid, iron and zinc may decrease the GI-absorption of lead which has been shown in animal experiments. In animal experiments concomitant intake of vitamin D, protein and fat may increase the uptake of lead. In man deficient iron status and alcohol may increase the GI-lead absorption.

## **2. BIOLOGICAL MONITORING OF INORGANIC LEAD**

Lead concentrations in blood are still the prevailing index of lead exposure and risk (US EPA 1986; Skerfving 1993). It is easy to obtain and the analyses are fairly uncomplicated. However, the interpretation of the results is hampered by the nonlinear relationship between lead exposure/uptake and B-Pb, both at inhalation and GI-exposure (US EPA 1986). There is also a nonlinear relationship between lead levels in other media, e.g. serum, urine and milk and B-Pb (Skerfving et al. 1993), as well as between different metabolic/toxic effects (e.g. on heme and nucleotide synthesis) and B-Pb. This is probably due to saturation of binding sites with high affinity within the erythrocytes (Skerfving and Bergdahl 2007). B-Pb seems to be a more sensitive index at low exposure levels than at high exposures.

The blood lead levels in unexposed subjects vary considerably. In Sweden, B-Pb in children without particular exposure is around 20 µg/L (Strömberg et al. 1995). A German Environmental Survey of environmental pollutants in

blood was conducted for the third time in 1998 including 4800 subjects with regard to region, community size, age (18 to 69 years) and gender. The geometric mean of Pb amounted to 31 µg/L. The geometric mean was higher in the blood of males than of females (36 µg/L versus 26 µg/L) (Becker et al. 2002). In many countries the levels are considerably higher than in Europe (Skerfving 1993).

Lead determinations in urine are a fairly widely used index of lead exposure. However, there is always a risk of external contamination if the samples are collected at work, and the available information as regards the relationship between exposure/effects and U-Pb is much more limited. The bone-Pb increases with increasing time of employment, from a few up to 100 µg/g or more (Somervaille et al. 1989; Nilsson et al. 1991; Gerhardsson et al. 1993). Thus, bone lead determinations may be a valuable index of long-term lead exposure. Bone lead determinations have been performed since the middle of the 1970's, mainly by X-ray fluorescence techniques. A <sup>57</sup>Co source has been used to excite the lead, and measure the characteristic K X-rays of lead (Ahlgren et al. 1976). In addition, <sup>109</sup>Cd has been used for measurements of lead in the tibia and calcaneus (Chettle et al. 1989). While these K techniques measure lead up to a considerable depth in the bone, L techniques mainly assess superficially located lead (Rosen et al 1991). In the K XRF-technique, an electron from the innermost K shell is excited by an incident photon in the X-ray region. Electrons from the L and M shells then move down to fill the vacancy in the K shell. The energy difference between the two shells appears as an X-ray, emitted by the atom. The X-ray spectrum acquired during the above process reveals a number of characteristic peaks. The energy of the peaks leads to the identification of the elements present in the sample (qualitative analysis), while the peak intensity provides the relevant or absolute elemental concentration (semi-quantitative or quantitative analysis) of lead. In the L XRF technique, electrons from the L shell are excited in a similar way and electrons from the M shell drop down to fill the vacancy. Thus, the resulting lead K- and L-alpha lines obtained with the two techniques, may not be directly comparable.

Significant relationships have been observed between bone lead levels at different bone sites (Somervaille et al. 1989; Gerhardsson et al. 1993; Skerfving et al. 1993). Lead mobilization from the skeleton may constitute a considerable source of endogenous lead exposure (Skerfving 1993). Lead concentrations in the skeleton may be a useful index of health risks, especially when related to chronic effects of lead exposure.

### 3. HEALTH EFFECTS

#### 3.1 *Nervous system*

Inorganic lead may cause symptoms and signs from both the peripheral and central nervous systems. This is due to demyelination, axonal degeneration, and possibly also presynaptic block. Damage to the peripheral nervous system may cause paralysis, as well as pain in the extremities. Chronic lead exposure may reduce nerve conduction velocity in peripheral nerves in adult subjects without clinical symptoms or signs of disease. In some studies, such effects have been recorded in subjects with B-Pbs as low as 1.5-2.0  $\mu\text{mol/L}$  (Skerfving 1993).

In animal experiments (Hoffer et al. 1987; Sundström and Karlsson 1987) and in humans, especially in children, lead exposure may cause encephalopathy, with ataxia, coma and convulsions (US EPA 1986). Impaired learning/memory abilities have been reported in rats with B-Pb levels of 0.72-0.96  $\mu\text{mol/L}$  (150-200  $\mu\text{g/L}$ ) and in non-human primates at B-Pb levels not exceeding 0.72  $\mu\text{mol/L}$  (150  $\mu\text{g/L}$ ). In addition, visual and auditory impairments have been reported in experimental animal studies.

In subjects without obvious clinical signs of encephalopathy, subjective and non-specific symptoms (e.g. fatigue, impaired concentration, loss of memory, insomnia, anxiety, and irritability) may occur, as well as impaired performance in psychometric tests. In such tests, minor effects, mainly of visual intelligence and visual-motor coordination, as well as changes of somatosensory-, visual-, and auditory-evoked potentials have been recorded in lead workers with B-Pbs as low as 2.0-2.5  $\mu\text{mol/L}$  (Skerfving 1993). These CNS-effects are, at least in some cases, partially reversible.

In rodents, CNS effects were associated with brain-lead levels in the order of 1-10 mg/kg (US EPA 1986). UK subjects without occupational exposure seem to have lead levels around 0.1 mg/kg. Occupationally exposed subjects have concentrations about 0.6 mg/kg (Barry 1975).

In general decreased global performance has been reported at B-Pbs > 400  $\mu\text{g/L}$  (Schwartz and Landrigan 1988; Landrigan et al. 1990). Seeber et al.

(2002) reviewed two different meta-analytical reviews on neurobehavioral effects based on 24 selected papers. The evaluation provides evidence for subtle effects associated with average blood lead levels between 370 and 520 µg/L. Thus the review supports the current German BEI of 400 µg/L.

### **3.2 Blood and blood-forming organs**

Lead has an inhibitory effect on steps in the chain of reactions that lead to the formation of heme, affecting e.g. the enzymes ALAD and ferrochelatase (heme synthetase). Lead also inhibits the activity of the enzyme pyrimidine-5-nucleotidase (P5N) in red cells. Heavy lead exposure is associated with reticulocytosis and occurrence of stippled erythrocytes in peripheral blood (US EPA 1986), possible mediated through the effect on P5N. Lead can also shorten the life-span of circulating erythrocytes, probably by inhibition of the Na<sup>+</sup>, K<sup>+</sup> ATPase, possibly also affecting the erythrocytes P5N, and by causing changes of membrane proteins. Anemia may follow of normocytic and sideroblastic type.

Lead inhibits several enzymes of heme synthesis in a dose-dependent manner. Inhibition of ALAD starts at B-Pbs around 0.5 µmol/L (Schütz and Skerfving 1976) and is complete at about 3 µmol/L. Inhibition of P5N occurs at similar levels. At B-Pb around 1.5 µmol/L, there is an increase of ZPP in a considerable fraction of the population (Skerfving et al 1993). Increases of ALA and CP in urine start at higher levels (Schütz and Skerfving 1976). There may be a risk of developing lead-induced anemia at B-Pbs in excess of about 500 µg/L (US EPA 1986; Silbergeld 1990; IPCS 1995). Subclinical changes in parameters of heme synthesis may occur below 400 µg Pb/L blood, but these findings are not regarded as being adverse.

### **3.3 Kidney**

Lead exposure may cause kidney damage (Lim et al. 2001). In acute lead toxicity, there is proximal tubular damage, which may result in a reversible Fanconi syndrome-like condition with aminoaciduria, glucosuria, and hyperphosphaturia. Further, the tubular damage may cause leakage of enzymes (e.g. the lysosomal NAG) from the cells into the urine (Skerfving 1993) at B-Pbs in the range 1.5-2.0 µmol/L. This effect may be reversible.

In experimental animals, prolonged exposure to lead may cause progressive irreversible nephropathy (Goyer 1989). In man, after heavy exposure for years, interstitial nephritis, with interstitial fibrosis, tubular atrophy, and arteriosclerotic changes may occur. Functionally, there is a decrease of renal plasma flow with a reduction of the glomerular filtration rate, resulting in azotemia (increase of blood urea nitrogen = BUN) and an increase of the tubular reabsorption of uric acid, resulting in an increase of serum levels of uric acid (eventually hyperuricemia), which is probably a cause of gout with arthritis (saturnine gouty arthritis; Skerfving 1993). Such changes seem to occur at B-Pbs of 2.5-3.0  $\mu\text{mol/L}$  or higher.

Rats developed proximal tubular damage at lead levels in the kidney around 45 mg/kg (Goyer et al. 1989). UK subjects without occupational exposure seem to have about 0.8 mg/kg in kidney cortex, occupationally exposed subjects about the same concentration (Barry 1975).

### **3.4 Gastrointestinal tract**

Lead exposure may cause a precipitation of dark-bluish lead sulfide in the gingiva (lead line; Burtonian line). Lead also affects the gastrointestinal tract, causing diarrhea, epigastric pain, nausea, indigestion, loss of appetite and colic (Skerfving 1993). Such symptoms and signs usually occur at B-Pbs higher than 3.5  $\mu\text{mol/L}$  (Skerfving and Bergdahl 2007).

### **3.5 Cardiovascular system**

In several studies of general populations, there were associations between blood pressure and B-Pb. However, all reported associations were weak, and a causal relationship has not been established since there are several possible confounding factors, as well as possibility of reverse causation (Skerfving 1993). There was an increase of the systolic and diastolic blood pressure by 1 to 2 mm Hg for each doubling of the B-Pb. Thus, there are indications of a leveling off of the effects as B-Pb increased. This may be the reason why the results in recent studies of lead workers have not been consistent (Skerfving 1993). In earlier studies of more heavily exposed workers, the observed blood pressure effects may depend on kidney damage with secondary hypertension. There was no increase of cardio- or cerebrovascular deaths

among smelter workers (Gerhardsson et al 1986), while glass workers had increased risks (Wingren and Axelson 1993).

Experiments have demonstrated effects of lead on the soft muscles of the vessels by interfering with the Na-K system, cAMP, Ca, and the renin angiotensin system. The theories have been mainly developed in animal experiments and in vitro tests. Lead may interfere with the renin-aldosterone axis and the kallikrein system and may have direct action at the level of the vascular smooth muscle and the potentiation of sympathetic stimulation. The available literature suggests a positive association between systolic blood pressure and the blood lead concentration. However, the correlation with diastolic blood pressure was much less consistent across the various studies.

Extrapolations from the multiple logistic regression models obtained in the Pooling Project and in the Framingham studies suggest that the observed 37 % decrease in mean blood lead concentrations in adult white males from 1976 to 1980 would lead to a 4.7% decrease of the incidence of fatal and nonfatal myocardial infarction over 10 years, a 6.7% decrease in the incidence of fatal and nonfatal strokes over 10 years, and a 5.5% decrease in the incidence of death from all causes over 11.5 years (Pirkle et al. 1985).

### **3.6 *Genotoxicity and carcinogenicity***

Lead acetate and lead subacetate caused kidney and brain tumors and lead phosphate caused kidney tumors in rodents following oral or parenteral administration (IARC 1987). However, the doses were high and caused gross morphological changes in the kidney. IARC (1987) concluded that there was sufficient evidence in experimental animals for the carcinogenicity of lead.

The potential carcinogenicity of lead has been investigated in a number of epidemiological studies in lead exposed workers. In 1995, Fu and Boffetta reviewed the epidemiological evidence on the carcinogenicity of inorganic lead, and combined the published data for meta-analysis. The results indicated a slight to moderate significant excess of deaths from stomach cancer, lung cancer, bladder cancer, and a non-significant excess from kidney cancer. The meta-analysis of studies dealing with industries with heavy exposure to lead such as lead battery industries and smelters produced

higher risks for cancer of the stomach, lung and kidney. Because of lack of data, however, it was not possible to control for potential confounders such as e.g. other occupational exposures, smoking and dietary habits. Even with this serious limitation, the increased relative risks support the hypothesis of an association between stomach and lung cancer and heavy exposure to lead. For bladder and kidney cancer, the excess risks are only suggestive of a true effect because of possible publication bias. A recent study of cancer mortality was performed in a cohort of 4518 lead smelter and battery workers (Wong and Harris 2000). A nested case-control study of stomach cancer was undertaken in this cohort, showing a significant increase of stomach cancer. This finding, however, was not related to the lead exposure.

In Finnish studies, 20 700 workers were followed by biological monitoring of lead in blood from 1973 to 1983 (Anttila et al. 1995). An increased risk of overall cancer incidence and lung cancer incidence was observed in this cohort in comparison with the Finnish general population. In a nested case-control study, the effect of several possible confounders (including smoking) was considered. The elevated lung cancer risk appeared to be magnified by concomitant exposure to lead and leaded engine exhaust (Anttila et al. 1995). The case-referent study included 26 nervous system cancers (16 gliomas). For glioma, the risk associated with the high exposure group was OR = 11.0. Adjustment for known confounders changed the results numerically without altering the overall picture (Anttila et al. 1995).

In 1987, IARC concluded that the epidemiological evidence was inadequate, whilst the data from animal experiments provide sufficient evidence of carcinogenicity. After consideration of the evidence of chromosomal damage in exposed workers, IARC classified lead as possibly carcinogenic for humans (group 2B). The carcinogenicity of lead was later re-evaluated at an IARC conference held in Gargnano, Italy (Landrigan et al. 2000). An update of the previously reported epidemiological meta-analysis by Fu and Boffetta (1995) supported the earlier findings (Steenland and Boffetta 2000). It was concluded that most of the epidemiological studies on the carcinogenicity of lead did not present an adequate dose-response pattern. The current evidence was regarded as somewhat supportive of an association between lung and stomach cancers and lead, but weaker in the cases of kidney cancer and brain cancer (Landrigan et al. 2000). Based on the results from the IARC conference in Gargnano, Italy, it was concluded that lead should be regarded as a proven animal carcinogen, and that the new data on

cancer risk of workers exposed to lead would probably justify a re-evaluation by IARC in the near future (Landrigan et al. 2000).

Due to experimental data, an indirect rather than direct genotoxic carcinogenic effect of lead has been indicated (Silbergeld et al. 2000). Thus, there may be a threshold for the carcinogenic effects in man that would argue in favor of setting health-based occupational exposure limits for lead.

### **3.6.1 Previous studies in lead smelter and battery workers**

Dingwall-Fordyce and Lane (1963) studied a cohort of 425 retired lead battery workers with at least 25 years of employment. The combined subcohort of employed and retired workers with a low work-related lead exposure showed an increased rate of observed versus expected deaths (25 vs 14.2;  $p < 0.05$ ). In high-lead exposed workers, however, no excess cancer deaths were recorded. Thus, no evidence was found to suggest that malignant neoplasms were related to lead exposure. In a case-control study of the deaths of 867 lead battery workers and 1206 controls during the period 1926 to 1985 no increased ratios of malignancies were reported, neither in general, nor for specific sites (Fanning 1988). In an English study (Malcolm and Barnett 1982), the mortality of 754 workers from a cohort of 1898 pensioners from four lead acid battery factories was determined. No excess rates for malignancies were observed in either subcohort. No dose-response pattern was found among the retired workers.

In an extended US study (Cooper and Gaffey 1975, Cooper 1976) a cohort of 7032 male lead smelter (six plants) and battery workers (10 plants), employed for at least one year during the period 1947 to 1970 was established. Increased standardized mortality ratios (SMRs) for malignant neoplasms were noted in both groups, 133 for smelter workers ( $p < 0.05$ ) and 111 (non-significant) for battery workers. The excess was largely attributed to tumours of the digestive and respiratory systems (not statistically significant). Most of the subjects, particularly those working in lead production facilities, had a multifactorial exposure including lead, sulphur dioxide as well as arsenic and cadmium, two potentially cancer causing metals. Furthermore, it was not possible to quantify the individual exposure to lead and to the other agents in most of the workers. No data on smoking habits were presented. A reanalysis of the data from this US study by Kang et al (1980) showed an increased incidence of deaths from all

malignant neoplasms (SMR 133;  $p < 0.01$ ), cancer of the digestive system (SMR 150;  $p < 0.02$ ) and the respiratory system (SMR 148;  $p < 0.03$ ) in lead smelter workers. For lead battery workers, an increased incidence of the two latter cancer forms was also observed (SMR 123;  $p < 0.04$  and 132;  $p < 0.02$ , respectively) but not for all malignant neoplasms (SMR 111;  $p > 0.05$ ).

In 1978, the 5490 members of the original cohort were observed for an additional five year period, 1971-1975 (Cooper 1981). The SMR of malignant neoplasms was lower than expected in smelter workers (18 observed vs 23.4 expected; SMR = 89) with an excess observed solely for respiratory tract cancers (9 observed cases vs 8.5 expected; adjusted SMR = 121). In the lead battery plant there were 71 deaths from malignancies vs 61 expected (adjusted SMR = 136;  $p < 0.05$ ). Raised ratios were observed for respiratory tract cancer (24 observed vs 21 expected; SMR = 128) and for other and unspecified sites (18 observed; 6.9 expected; SMR = 293). The author concluded that the follow-up study did support a carcinogenic role for lead. A large portion of the malignant neoplasms, especially in lead battery workers was due to cancers of unknown origin. Individual exposure data were lacking as well as information about smoking habits. An excess of heavy smokers among the workers may be the reason for the raised figures for lung cancer. Later, Cooper (Cooper et al 1985, Cooper 1988) made a new follow-up from 1947 to 1980 of this US cohort, including 4519 battery plant workers and 2300 lead production and smelter workers. The SMR for all malignant neoplasms was 113 in both cohorts, but significantly raised only for battery workers (344 observed vs 303.4 expected; 95 % CI 102-126). The digestive and respiratory systems were responsible for most of the excess cancer deaths in both cohorts, but significantly raised SMRs were observed only for gastric (34 observed vs 20.2 expected; SMR 168; 95 % CI 116-235) and lung cancer (109 observed vs 87.8 expected; SMR 124; 95 % CI 102-150) in battery plant workers. The workers had a multifactorial exposure. Individual exposure data was meagre up to 1960. Urinary lead data were available for 2275 men and blood lead data for 1860 men (about 30 % of the populations), who participated in a lead biomonitoring program in the period 1947-1972. Data on possible confounding factors such as smoking habits, alcohol consumption, diet habits and ethnicity were lacking.

The latest follow-up of this US study was made by Wong and Harris (2000). The cohort was based on 4519 lead battery workers and 2300 lead smelter workers. The follow-up also included a nested case-control study of stomach cancer (30 cases and 120 age-matched controls). The study showed a

significantly increased mortality for stomach cancer (SMR = 147; 95 % CI 113-190), lung cancer (SMR = 116; 95 % CI 104-130) and cancer of the thyroid and other endocrine glands (SMR = 308; 95 % CI 133-607). No dose-response pattern was noted for lung cancer. The increased SMRs may be explained by confounding from smoking. The elevated SMR for cancer of the thyroid and other endocrine glands must be interpreted with caution according to the authors due to the small number of deaths and lack of information about other concomitant exposures as well as potential confounding factors. The nested case-control study did not show any increased odds ratios for the various exposure indices investigated. No dose-response pattern between stomach cancer and lead exposure was observed. Thus, the observed increased SMR for stomach cancer was probably not associated with lead exposure. The mortality for kidney cancer, bladder cancer, cancer of the central nervous system, lymphatic and hematopoietic cancer was not increased.

Rencher et al (1977) studied the mortality at a large western US copper smelter during the period 1959 to 1969. Smoking habits were known for more than 90 % of the population. About 60 % of the workers at all plants investigated were smokers. Seven percent of all deaths at the smelter were due to lung cancer as compared with 2.7 % for the state. No synergistic effect was found for smoking. Those who died of lung cancer had the highest cumulative exposure indices for SO<sub>2</sub>, H<sub>2</sub>SO<sub>4</sub>, As, Pb and Cu. The differences were statistically significant for the exposures to SO<sub>2</sub>, As and Pb. The increased death rates for lung cancer may have been caused by previously high arsenic exposure at the smelter. In an Australian study (McMichael and Johnson 1982), 241 male smelter workers diagnosed with lead poisoning during the period 1928-1959 were identified. Age-standardized proportional mortality rates (SPMR) were calculated after comparisons with the mortality pattern in 695 other workers at the same smelter and with the Australian male population. For cancer, low SPMRs were obtained. No increased risk of cancer was detected at the smelter.

Selevan et al (1985) studied the mortality in a cohort of 1987 males employed between 1940 and 1965 at a primary US lead smelter. Other exposures included zinc, cadmium, arsenic, SO<sub>2</sub>, and in some departments also airborne free silica. Comparison was made with the general US white male population based on figures from the National Center for Health Statistics and the US Census Bureau. The overall mortality in malignant diseases was not elevated (SMR = 95; 95 % CI 78-114), neither was the

mortality for respiratory cancer (SMR = 111; 95 % CI 80-151). Six renal cancers were observed, giving a non-significantly raised SMR of 204 (95 % CI 75-444). The power for detecting a doubling of the lung cancer mortality was 98 % in this study. Smoking habits were not known. In an extended follow-up study of this cohort (Steenland et al 1992), 1990 male hourly smelter workers were identified. They had worked in a lead-exposed department for at least one year, with at least one day of employment at the smelter between 1940 and 1965. The US population was used as a reference group. In the entire cohort 9 kidney cancers were observed giving a SMR of 193 (95 % CI 88-367). The SMR in the subcohort with high lead exposure was further increased giving a marginally significant SMR of 239 (95 % CI 103-471), which was based on 8 observed kidney malignancies. Detailed data about individual lead exposures were lacking as well as information about potential confounders such as concomitant exposure to cadmium, arsenic and other exposures at the primary smelter. Furthermore, smoking data were lacking.

The lung cancer mortality was investigated in a British cohort study of men employed at a zinc-cadmium smelter (Ades and Kazantzis 1988). The study comprised all hourly paid male workers employed at the smelter on 1 January 1943 and those who subsequently started to work before 1970. They had to be born before 1940 and had to have worked for at least one year before 1970 to be included in the investigation. In total, 4173 men of whom 174 died of lung cancer were followed up for more than 10 years. SMRs were calculated after regional comparisons. The lung cancer mortality was positively related to time of employment and also to the cumulative arsenic and lead exposure, but not to cumulative cadmium exposure. It was not possible, however, to elucidate the separate cause-effect relationships for arsenic, lead or for other concomitant exposures at the smelter. Furthermore, smoking data were only known for a minor fraction (N=274) of the study group.

Gerhardsson et al (1995) studied the mortality and cancer incidence among lead workers at a secondary lead smelter in southern Sweden. The cohort consisted of 664 male lead smelter workers, employed for at least three months from 1942 to 1987. The causes of death 1969-1989 were obtained from Statistics Sweden. The death certificates were coded according to the 8<sup>th</sup> revision of the international classification of diseases (ICD-8). Yearly incidences for cancer from 1969 to 1989 were obtained from the National Swedish Tumour Registry, with calendar year, sex and five-year age group

specific incidences for the county population. A slightly increased mortality was noted for all malignancies (SMR 165; 95 % CI 109-244). The incidence of GI cancers was barely significant in the quartile with the highest cumulative blood lead exposure (SIR 2.34; 95 % CI 1.07-4.45). The risk estimates did not show a dose-response pattern and were not associated with latency time but were related to employment before 1970. The results must be interpreted with caution due to small numbers, and lack of dietary and smoking data. In an Italian study the mortality among 1345 male smelter workers at a lead and zinc smelting plant was followed from 1973 to 1991 (Cocco 1996). Death certificates were provided for all deceased subjects by the Local Health Units. Standardized mortality rates were calculated after comparison with death rates in the general Sardinian male population. No significant excess mortality was noted for any single cancer site. The lung cancer mortality was lower than expected, 2 observed cases vs 3.5 expected. The study is hampered by limited numbers, low statistical power, lack of detailed information about individual exposures to lead, zinc and other substances at the smelter, as well as lack of smoking data.

Later, Cocco et al (1997) studied 1388 lead workers at an Italian lead-smelting plant. Vital status of the workers was followed from 1950 to 1992. Fifty-five percent of the cohort members (771 of 1388) had died by the end of follow-up. Death certificates were available for 96 % of the deceased men. The underlying causes of death were coded due to the 9<sup>th</sup> revision of the International Classification of Diseases (ICD-9). Standardized mortality rates were calculated for specific causes of death after comparison with national and regional reference rates. Mortality rates for all cancers, stomach cancer and lung cancer were lower than expected. Non-significantly raised SMRs were noted for genitourinary and kidney cancers. The risk ratios, however, increased significantly by duration of employment. The study was hampered by limited power and concomitant exposure to other agents, e.g. cadmium. Furthermore, smoking data were lacking.

### **3.7 Reproductive effects**

Lead exposure may impair the endocrine function of male animals, probably through disturbance of the hypothalamic-pituitary function (Erfurth et al. 2001). Furthermore, lead has been shown to induce testicular atrophy, and to reduce spermatogenesis, affect the spermatozoa and to reduce sperm motility (US EPA 1986; Skerfving and Bergdahl 2007).

In female animals, lead may disturb the hypothalamus-pituitary-ovarian-uterine function (Govoni et al 1984) causing altered menstrual cycles. Implantation problems may appear. Furthermore, lead exposure may decrease the blood flow through the placenta and affect the heme metabolism of the fetus (US EPA 1986).

Several studies suggest an increased risk of spontaneous abortion, perinatal death and low birth weight following paternal occupational lead exposure (Lindbohm et al. 1991; Kristensen et al 1993; Anttila and Sallmén 1995; Min et al 1996). In a Finnish study, a significant increase was observed for spontaneous abortion among the wives of men whose blood lead concentrations were  $\geq 300 \mu\text{g/L}$  during spermatogenesis (Lindbohm et al. 1991). Reduced fertility has also been observed among men with long-time lead exposure (Lin et al 1996). From a recent review on male reproductive toxicity of lead (Apostoli et al. 1998) it seems evident that only Pb levels exceeding  $400 \mu\text{g/L}$  in blood are associated with a decrease in sperm count, volume and morphological alterations.

An evaluation by (Skerfving 1993 and Skerfving and Bergdahl 2007) indicates that slight effect in the pregnant women, newborn (cord blood) and/or infant may be present at BPbs in the range of  $100\text{-}150 \mu\text{g/L}$ . However, the interpretation of these studies is complicated by several methodological problems.

#### **4. HAZARD EVALUATION AND LIMITING CONCENTRATIONS**

The main toxic effect of lead in males and females is impairment of neurobehavioral test performance. Other critical endpoints of lead toxicity include toxicity to the nervous system and the kidneys. Based on experimental findings it seems plausible that lead has no direct genotoxic effects, which argues for establishing a practical threshold limit value for lead toxicity. Thus, an OEL based on avoiding functional CNS alterations is expected also to protect versus toxicity to the PNS and the kidney, including possibly the development of renal cancer.

There is still considerable uncertainty concerning the impairment of reproductive function by lead. For males, there are several studies indicating

that only B-Pb levels above 400  $\mu\text{g/L}$  are connected with impairment of fertility.

A biological limit blood lead value of 300  $\mu\text{g/L}$  has been suggested in both males and females by SCOEL (2003). The committee also suggested an occupational exposure limit (OEL) of 100  $\mu\text{g Pb/m}^3$ . A TLV-TWA of 0.05  $\text{mg/m}^3$ , measured as lead is recommended in the US for occupational exposure to lead and its inorganic compounds based on the BEI of 300  $\mu\text{g/L}$  for lead. This value is intended to minimize the potential for adverse health effects that may include blood dyscrasias, peripheral neuropathies, kidney effects, effects on the spermatogenesis, impaired intellectual development in children during gestation, and carcinogenicity (ACGIH 2006). According to ACGIH (2001), long-term exposure in adults causing B-Pbs  $\leq 400 \mu\text{g/L}$  should minimize the risk for adverse effects. Meticulous plant housekeeping, strict personal cleanliness, and prohibition of eating, drinking and smoking in lead-contaminated areas are very important (ACGIH 2001). Women of child bearing potential, whose blood Pb exceeds 100  $\mu\text{g/L}$ , are at risk of delivering a child with a blood Pb over the current Centers for Disease Control guideline of 100  $\mu\text{g/L}$ . If the blood Pb of such children remains elevated, they may be at risk of developing cognitive deficits. Thus, the B-Pb of these children should be closely monitored and appropriate steps should be taken to minimize the child's exposure to environmental lead (ACGIH 1998). In Germany, the MAK value for lead and lead compounds is 0.1  $\text{mg/m}^3$ . The corresponding BAT/BEI value is 400  $\mu\text{g Pb/L}$  in whole blood (MAK 2006; 100  $\mu\text{g Pb/L}$  for females  $< 45$  years of age). In Sweden the TLV for lead in total dust is 0.1  $\text{mg/m}^3$ , in respirable dust 0.05  $\text{mg Pb/m}^3$ . The corresponding BEI is 2.0  $\mu\text{mol/L}$  (1.2  $\mu\text{mol/L}$  for females  $< 50$  years of age).

Biological monitoring of lead exposure has several advantages over external exposure assessment. Traditionally, levels in blood (B-Pb) have been widely employed. However, a problem with B-Pb is a saturation of the erythrocyte lead concentration, which causes a nonlinear relationship between uptake and B-Pb, and also between metabolic/toxic effects and B-Pb. During the 1990's, determinations of lead in plasma has been suggested as an alternative of blood lead determinations, as it may be a more accurate index of lead exposure and risk than B-Pb. During the last decades, techniques for in vivo determination by XRF of lead in fingerbone, tibia, or calcaneus have become available. These bone lead determinations have been used to assess

the previous lead exposure of an individual or a group, as well as the contribution from the endogenous lead exposure

## **5. ARSENIC**

### ***5.1 Occurrence, use, exposure to inorganic arsenic***

Arsenic can be classified into three groups: inorganic arsenic compounds, organic arsenic compounds and arsine gas. The earth's crust contains about 3.4 ppm arsenic, usually in the form of sulfide. Arsenic trioxide (white arsenic) is a well known by-product, which is obtained in smelters when handling copper, lead and gold ores. The average annual world production of arsenic in the mid 1970's was about 60 000 tons (WHO 1981).

Arsenic has been used as a therapeutic agent for treatment of e.g. leukemia, psoriasis and bronchial asthma. Major arsenic uses include pesticides (e.g. lead arsenate, calcium arsenate) and wood preservation (e.g. copper chromium arsenate). Arsenic has also been used for the production of glass and dyestuffs, and for the production of several alloys to increase their hardness and heat resistance. Gallium arsenide and indium arsenide have been used in semiconductors, solar cells and space research (IARC 2006, Fowler et al 2007).

### ***5.2 Metabolism of arsenic in man and animals***

#### **5.2.1 Absorption**

##### **5.2.1.1 Inhalation**

Data about the deposition and absorption of inhaled arsenic in humans are scanty. In smelter workers exposed to arsenic trioxide dust, about 40-60 % of the estimated inhaled dose was excreted in urine (Vahter et al 1986). Absorption of arsenic trioxide dusts and fumes as estimated by urinary metabolites, correlated with the time weighted average arsenic air concentrations from personal sampling in the breathing zone (Offergelt et al

1992). A slower uptake has been reported for slowly soluble substances such as arsenic sulfide and lead arsenate (Marafante and Vahter 1987).

### **5.2.1.2 Ingestion**

Animal and human data indicate that more than 90 % of an ingested dose of dissolved inorganic trivalent or pentavalent arsenic is absorbed in the GI tract (Marafante et al 1981m Zheng et al 2002). The absorption can be considerably lower if highly insoluble forms of arsenic are ingested and affected by factors such as particle size and pH of the gastric juice.

### **5.2.1.3 Skin**

Systemic toxic effects have been reported from occupational accidents where arsenic acid or arsenic trichloride has been splashed on the skin of workers (Garb and Hine 1977). No quantitative data are, however, available regarding a possible absorption of inorganic arsenicals in humans after dermal exposure.

## **5.2.2 Distribution**

After absorption by the lungs or the GI tract, arsenic is transported via the blood to different organs. A substantial part of the absorbed arsenic is bound to hemoglobin in the red blood cells. Exposure to arsenite or arsenate gives an accumulation in the liver, kidneys and lung but also in muscle, heart, spleen, pancreas and brain (Benramdane et al 1999). Long-term retention of arsenic has been reported in hair, skin, squameous epithelium of the upper GI tract, epididymis, thyroid, lens and skeleton (Lindgren et al 1982). Human autopsy data have also shown high arsenic levels in hair, nails, teeth, bone, and skin (Yukawa et al 1980). Arsenite exposure seems to give higher concentrations in most tissues as compared to arsenate (Vahter and Marafante 1983).

### 5.2.3 Elimination

The major part of absorbed inorganic arsenic is excreted via the urine. Only a few percent is excreted in feces (Apostoli et al 1999). The trivalent arsenic compounds are formed in vivo after exposure to pentavalent arsenic. Arsenic is metabolized by a series of reductions and oxidations and by methylation reactions. The primary forms of arsenic observed in the urine after inhalational exposure are DMA and MMA, while inorganic arsenic constitutes < 25 % of the total urinary arsenic (Apostoli et al 1999). At low exposure levels, urinary arsenic levels generally show a linear increase with increasing arsenic intake (Calderon et al 1999). In the case of continuous human intake over a few days, 60-70 % of the daily dose is excreted in urine (Buchet et al 1981b).

## 6. BIOLOGIC MONITORING OF INORGANIC ARSENIC

After arsenic intake in humans, the whole body clearance has a half-time of 40-60 hours in humans (Buchet et al 1981b). After oral intake of radiolabeled pentavalent arsenic, 66 % was excreted with a half-time of 2.1 days, 30 % with a half-time of 9.5 days and 3.7 % with a half-time of 38 days in the three phases (Pomroy et al 1980).

Normal levels of arsenic in urine in occupationally unexposed populations range between 5-50 µg/L (Buchet et al 1980). Arsenic concentration in urine may be used as an index of exposure but the interpretation of the data has to consider a number of factors, e.g. diet (seafood), the time between exposure and urine sampling. Analytical speciation can be used to analyze the concentrations of inorganic arsenic and its metabolites MMA and DMA in relation to organic arsenic forms (Buchet et al 1980, Norin and Vahter 1981).

Normal concentrations of arsenic in blood may range between 1-2 µg/L (Concha et al 1998b). Arsenic levels in hair in subjects without occupational exposure can range between 0.02-8.17 mg/kg (Liebscher and Smith 1968). The levels reflect the degree of arsenic pollution in the community (Bencko and Symon 1977). A major problem is the difficulties to distinguish between arsenic absorbed onto hair from external contamination and arsenic incorporated into hair from the internal body burden. Therefore, caution is needed when using hair as an indicator of absorbed arsenic, if the external contamination cannot be controlled (Vahter et al 1983).

## **7. HEALTH EFFECTS OF INORGANIC ARSENIC**

### **7.1 Acute and subacute effects**

The lethal dose in humans after ingestion is approximately 1-3 mg/day. Acute and subacute effects include gastrointestinal, dermal, nervous, renal, hepatic, hematologic, cardiovascular, respiratory and ophthalmic systems. The GI-symptoms often start with metallic or garlic-like taste followed by dry mouth, burning lips and dysphagia. Later decrease in blood volume, blood pressure, electrolyte imbalance and shock may follow. In the kidney the sites of damage include capillary, tubules, and glomeruli. Neuropathy is mainly due to axonal degeneration (IARC 2004).

### **7.2 Chronic effects**

Classical cutaneous manifestations include hyperpigmentation with depigmentation and palmoplantar hyperkeratosis (IARC 2004). Dose-related skin changes in subjects consuming arsenic contaminated drinking water has been reported from e.g. Bangladesh by Ahsan et al (2006). Long-term low-dose exposure to ingested arsenic may cause a variety of GI symptoms, e.g. gastroenteritis, dyspepsia, nausea, diarrhea, anorexia, and abdominal discomfort (IARC 2004). Polyneuropathy is inconsistently reported in individuals with chronic low-grade arsenic exposure.

The main source of environmental exposure to arsenic for the general population is the intake of contaminated drinking water. High concentrations up to 5000 µg/L have been found in different parts of the world, e.g. around the Gulf of Bengal, in South America and in Taiwan (Boffetta 2004). Chronic exposure to arsenic in drinking water can lead to liver cirrhosis, portal hypertension and fatty degeneration (IARC 2004). An increased mortality from arsenic exposure has also been reported among arsenic-exposed copper smelter workers (Axelson et al 1978). Hematologic changes include normochromic normocytic anemia, megaloblastic anemia, granulocytopenia, thrombocytopenia, aplastic anemia, and myelodysplasia. Inhalational exposure to arsenic containing dust or fume may cause rhinitis, pharyngitis, laryngitis, tracheobronchitis, chronic cough, crepitation, shortness of breath, and restrictive as well as obstructive lung disease (IARC

2004). Arsenic exerts its toxicity by inactivating up to 200 enzymes, predominantly those that are involved in cellular energy pathways and DNA synthesis and repair (Ratnaïke 2003). Metabolic effects include an increased prevalence of diabetes mellitus (Rahman et al 1999, Tsai et al 1999). Chronic cardiovascular effects include QT-prolongation and increased dispersion, peripheral, coronary and cerebral artery diseases (e.g. cerebral infarction), arrhythmias, carotid atherosclerosis, hypertension and microcirculation abnormality (IARC 2004). Both ingested and inhaled inorganic arsenic has been associated with an increased mortality from cardiovascular diseases, especially ischemic heart disease (IARC 2004). Blackfoot disease is a well-known effect of long-term arsenic exposure. It is characterized by a severe systemic arteriosclerosis in combination with dry gangrene and spontaneous amputations of affected extremities and end stages (Chen et al 1988b). The development of the disease has been thoroughly described in an endemic area in southwestern Taiwan, where the inhabitants have used drinking water with a high arsenic concentration for more than 50 year (Tseng 1977).

High concentrations of arsenic in drinking water have been observed in large regions of Bangladesh, China and West Bengal (India) and in smaller areas of Argentina, Australia, Chile, Mexico, Taiwan, the USA and Viet Nam. The arsenic concentrations ranged from tens to thousands of  $\mu\text{g/L}$ . Ecological, case-control and cohort studies have shown a significant dose-response pattern between arsenic concentrations in drinking water and increased risks of cancers of liver, nasal cavity, lung, skin, urinary bladder, kidney and prostate in Taiwan (Tsai et al 1999, Boffetta 2004, Chen et al 2004, Navarro et al 2007). The effects may be influenced by age, gender and body mass index (Ahsan et al 2006). Increased risks for lung cancer has been observed in ecological, case-control and cohort studies in Taiwan, Japan, Chile and Argentine. A strong association was found in populations with high arsenic exposure (IARC 2004). An increased proportion of squamous cell and small cell lung carcinomas have been found in areas with arsenic contaminated drinking water (Guo et al 2004). Based on the sufficient evidence in humans that arsenic in drinking water causes cancers of the urinary bladder, lung and skin, arsenic in drinking water has been classified as a group 1 carcinogen to humans (IARC 2004).

A large number of skin cancers have been noted in subjects exposed to inorganic arsenic through drugs, drinking water or pesticides. Based on mortality data from residents in an endemic area of arsenic exposure in

southwestern Taiwan (Chen et al 1992), the life-time risks of developing cancer of the lung, liver, bladder and kidney have been calculated to 1 µg/kg/day of inorganic arsenic due to ingestion. Several case-control and cohort studies in smelter workers have shown a significantly raised mortality from respiratory cancer among the exposed workers. Long-term exposure to inorganic arsenic through inhalation and ingestion, e.g. in copper smelters, show a dose-response relationship to the risk of developing cancers of the lung and nasal cavity (Pinto et al 1978, Enterline and Marsh 1982, NRC 1999, IARC 2004). An increased mortality at a UK tin smelter has been attributed to concomitant exposure to arsenic (Jones et al 2007).

In animal studies on Syrian golden hamsters arsenic and cigarette smoke have been found to synergistically increase the DNA oxidation in the lung (Hays et al 2006). An interaction between inhaled inorganic arsenic and cigarette smoking for the development of lung cancer has been reported by Jarup and Pershagen (1991). The increased risk of developing lung cancer may also appear in arsenic exposed non-smokers (Neuberger and Field 2003).

The genotoxicity of arsenic is mainly caused by trivalent arsenicals, which may interact with cellular targets such as proteins and DNA (Kitchin 2001). In humans, arsenic is a human chromosomal carcinogen. Elevated frequencies of micronuclei, chromosomal aberrations and aneuploidy have been observed in peripheral lymphocytes and/or urothelial cells in subjects exposed to raised concentrations of arsenic. In vitro, arsenic has caused various types of chromosomal mutations and aneuploidy (IARC 2004). Biomarkers of early biological effects of ingested inorganic arsenic include blood concentrations of reactive oxidants and anti-oxidants, genetic expression of inflammatory molecules as well as cytogenetic changes including sister chromatid exchange, micronuclei, and chromosome aberrations of peripheral lymphocytes (Chen et al 2005).

## **8. THE RONNSKAR SMELTER**

### ***8.1 History, processes and products***

The Ronnskar smelter was built from 1928 to 1930 to extract metals from the Boliden mine that was discovered in 1924. The first copper ingot was cast in 1930. The smelter is situated in Skelleftehamn, about 17 km from the city of Skelleftea, on the tip of a peninsula protruding into the sea of Bothnia. From the start only the ore from the Boliden Mine was processed.

This ore had a complex composition with a high concentration of arsenic. Thus, conventional processing methods could not be applied and accordingly new process technologies had to be developed. Processes and products at the smelter from the 1980's are presented in Figure 1.

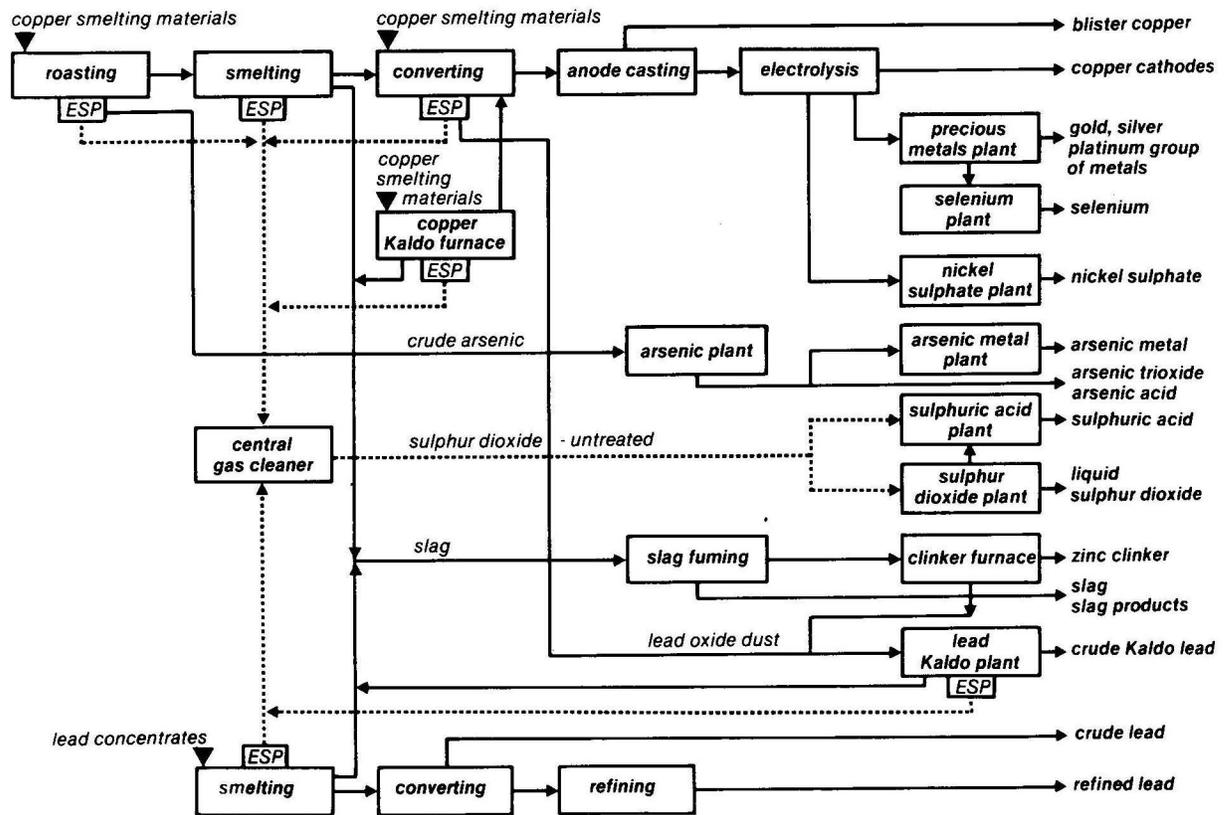


Figure 1. Processes and products at the Ronnskar smelter. ESP = Electrostatic precipitators. Courtesy: New Boliden AB.

The arsenic refinery plant was constructed in 1933 and a new arsenic plant was built in 1962. In the middle of the 1970's a new arsenic metal plant was opened. The arsenic production then went on to 1991, when the arsenic plant was closed. The lead plant was built in 1942, and the lead production started in 1943. In 1976 the lead Kaldo plant was constructed. In 1989 the original lead plant was closed and thereafter all lead production has taken place at the lead Kaldo plant.

The raw materials that are used by the smelter are primarily concentrates, consisting of sulfide minerals. In addition significant quantities of scrap and other secondary materials are used for the production of copper (Figure 1).

### **8.1.1 Copper**

The smelter produces blister copper (crude copper) by a conventional process consisting of roasting, smelting and converting. Blister copper contains about 98 % of copper and is used for refining into electrolytic copper with a copper content of 99.995 %.

### **8.1.2 Lead**

In the production of lead, the smelter uses primarily lead concentrates and also flue dust containing lead, obtained as a by-product from the Company's plant for the production of copper and zinc clinker. The two main processes that are used for the lead production, flash smelting and the Kaldo technique, are both developed by the Company. In flash smelting, the concentrate is smelted in an electric furnace without prior roasting or sintering. The furnace lead is then converted and refined to a purity exceeding 99.99 %. In the Kaldo technique, all process stages take place in the same reactor, the Kaldo furnace. Pelletized flue dust, slag-forming agents and coke are charged and smelted. After smelting, the lead, arsenic, antimony and tin compounds are reduced to the corresponding metals and are predominantly collected in the bullion. The zinc and the iron content are eliminated in the slag which is transported in molten form to the slag fuming plant for recovering the zinc content. The bullion is refined to remove the arsenic by the addition of iron. The iron and arsenic form a compound (speiss) which is separated. The remainder is crude Kaldo lead which contains 96-98 % of lead, as well as tin, antimony and silver etc.

### **8.1.3 Other products**

Several other metals are extracted as by-products, e.g. silver, gold, platinum and palladium as well as selenium and nickel. Other important by-products are crude arsenic, arsenic metal, arsenic trioxide, arsenic acid, zinc clinker, sulphur, sulphuric acid and liquid sulphur dioxide (Figure 1).

## **9. TECHNICAL PREVENTIVE MEASURES**

The work environment at the Ronnskar smelter has changed dramatically since the beginning of the production in 1930 (Nygren 1980, Gerhardsson 1986, Sandstrom 1992). Electric trucks were introduced in 1937. During the 1940's local exhausts were built over the roasters. Cyclones (dust collectors) separated the dust from the furnace gases. The elevators for the roasted material were rebuilt in 1949 (Gerhardsson 1986). The electric smelting processes and an improved ventilation system significantly reduced the exposure (Nygren 1980).

The copper smelting department was rebuilt in the late 1940's and the transport system for the roasting was improved (Sandstrom 1992). In 1949 the converter hall was reconstructed and eight converters were replaced by two bigger ones with a higher capacity (Gerhardsson 1986). A new gas purification system was introduced in 1953 and rebuilt in 1975. A new electrolysis plant was built in 1958 and a new arsenic plant in 1962. A new arsenic metal work was opened in 1974 and in 1976 the lead Kaldo plant started its production. The lead plant was thoroughly modernized in 1979-1981 (Gerhardsson 1986). In 1978, a new vacuum system was added (Sandstrom 1992). In 1980, a fluidized bed roaster replaced four older furnaces.

The electrolysis plant was rebuilt and expanded in 1985. In 1989, all lead production moved to the lead Kaldo plant. The arsenic plant was closed in 1991. In 1998-2000 the smelter was totally rebuilt, expanded and modernized through an investment of 2 billion SEK. The lead refinery plant was modernized in 2002.

During the Second World War, personal breathing protective devices were more systematically introduced. Their use gradually increased during the 1950's and 1960's.

## **10. EARLIER STUDIES OF RONNSKAR EMPLOYEES**

The first study at the smelter, that was initiated and financed by the labour union, was performed by Inghe and Bursell (1937). They compared the registered sick-leaves in 499 smelter workers with a control group of 98 workers from the nearby wood-pulp mill at Klemensnas. In 1932, the registered sick-leaves at the roasters, flame ovens, converter hall and the

arsenic plant ranged from 10.7 to 20.8 days per 100 working shifts. Because of preventive measures undertaken, the overall registered sick-leaves decreased from 8.7 days per 100 shifts in 1932 to 0.9 days per 100 shifts in 1937. The disease pattern was dominated by bronchitis, tracheitis, laryngitis, ulcer and perforations of the nasal septum, rhinitis and dermatitis. At the arsenic plant 25 % of the workers (n=34) suffered from perforations of the nasal septum. About 60 % of the workers complained about fatigue compared to 9 % among the referents.

In 1947, Sjostrand examined 20 selected workers at the Karolinska Hospital, Stockholm. Seventeen of these workers showed chronic changes in the respiratory tract characterized by mucous membrane atrophy, with or without redness and a coating of tough mucus in the lower respiratory tract. Several studies at the smelter was undertaken by the Swedish National Institute of Public Health in the 1940's and 1950's. Forssman et al (1949) observed objective changes in the upper and lower respiratory airways such as hyperplasia or atrophy of the mucous membranes and perforation of the nasal septum. Impairments of the lung function were registered by spirometry. After an extensive study of 1459 workers, Lundgren et al (1951) defined a disease at the smelter which was named "Morbus Ronnskar" It was characterized by a chronic rhino-pharyngo-tracheo-bronchitis with atrophy of the mucous membranes in the respiratory passages and secretions of the thick mucus, emphysema and impaired pulmonary function (Lundgren et al 1951, Lundgren 1954, Warfvinge 1968). Arsenic trioxide and sulphur dioxide were supposed to be the most important etiologic factors.

From 1932 to 1948 a total of 1 462 sick-leaves caused by arsenic dermatitis was reported. The skin changes were studied by the Company health physician Ivar Holmqvist. In his medical dissertation (Holmqvist 1951) he described them as being of the eczematous type with erythema, swelling and papules or vesicles, or of the follicular type with erythema and follicular swelling or follicular pustules. In the 1960's, Holmqvist reported the first lung cancer cases that seemed to be related to work. This clinical observation was verified in a case-referent study from the smelter by Axelson et al (1978) showing a five-fold increase of the lung cancer mortality and a two-fold increase of the cardiovascular disease among the smelter workers. A dose-response relationship to arsenic was shown.

In a comprehensive retrospective cohort study Wall (1980) reported an excess total mortality of 18 % for Ronnskar smelter workers relative to the

general population. Excess figures for tumours and circulatory diseases were 39 % and 32 % respectively. For tumours the increased mortality was mainly due to lung cancer, for which the risk was three-fold compared to the general population and 5-fold relative to local populations. Cerebrovascular diseases showed an elevated risk of 60-70 %. Dose-response analyses clearly indicated that the roasters and the arsenic plant were particular risk-places for cancer, especially lung cancer.

In a case-referent study Pershagen et al (1981) reported an age standardized rate ratio (SRR) for death from lung cancer of 3.0 for arsenic non-smokers, 4.9 for nonarsenic exposed smokers and 14.6 for arsenic exposed smokers, which indicates a multiplicative effect (non-arsenic exposed non-smokers = 1.0). Eighty-five percent of all deaths from lung cancer among the smelter workers were attributable to arsenic exposure or smoking or both. Rehnlund et al (1980) performed a lung-cytologic investigation of highly exposed workers. The authors found a significant relationship between tobacco smoking and marked atypies by multivariate analysis. The histological types of lung cancer were further investigated by Pershagen et al (1987) comparing 93 arsenic exposed smelter workers with 136 patients from the county where the smelter was located. No pronounced differences in the histological types were, however, noted.

In 1989, Jarup et al studied a cohort of 3916 smelter workers, employed for at least three months from 1928 through 1967. SMRs were calculated using age-specific mortality rates from the county where the smelter was situated. A positive dose-response relationship was observed between cumulative arsenic exposure and lung cancer mortality with an overall SMR of 372 (304-450; 95 % CI). The lung cancer mortality was related to the estimated average intensity of exposure to arsenic, but not to the duration. Smoking histories were collected for 107 lung cancer cases and 214 controls from the cohort. Lung cancer risks were positively related to cumulative arsenic exposure with smoking standardized relative risks ranging from 0.7 to 8.7 in different exposure groups. The interaction between arsenic and smoking for the risk of developing lung cancer was intermediate between additive and multiplicative and was less pronounced among heavy smokers (Jarup et al 1991).

Sandstrom et al (1989) studied trends in the incidence of cancer using five year calendar periods. The authors found a decreasing rate of lung cancer during the period 1976-1980, both for mortality and incidence. The cohort

was then expanded, comprising 6334 blue collar workers, first employed 1928-1979. They were followed-up in the cancer register up to January 1<sup>st</sup>, 1987 and in the cause-of-death register up to January 1<sup>st</sup>, 1988. The follow-up study also showed a decreasing trend in lung cancer incidence and mortality among the workers who, however, still showed an elevated lung cancer incidence as compared with Swedish males (Sandstrom et al 1992). An interaction between smoking and work at the roasters was reported by Sandstrom and Wall (1995).

The occurrence of chromosomal aberrations in cultured lymphocytes of workers at the smelter exposed to arsenic and lead has been examined by Beckman (1978). Nordenson et al (1978) observed an increased frequency of both chromosome breaks and achromatic regions (so-called gaps). An antagonistic (protective) effect of selenium against arsenic, lead, or sulphur dioxide (SO<sub>2</sub>) in human lymphocyte cultures was shown by Beckman and Nordenson in 1986. No synergistic effects were found, and the interactions between arsenic, lead and SO<sub>2</sub> were mainly antagonistic. The authors concluded that these unexpected findings indicated that mixed exposure, where arsenic, lead, and SO<sub>2</sub> are involved, may cause less genetic damage than expected (Beckman and Nordenson, 1986). No effects on birth weight and the risk of perinatal death among the offspring of parents living near the smelter or among those employed at the smelter have been found (Wulff et al 1995). Neither a general nor a specific significantly increased risk of congenital malformation was observed in a study of 2724 children born to women living close to the smelter or to employees of the smelter as compared with 15191 children in a reference population (Wulff et al 1996). Furthermore, Wulff et al (1997) found no environmental effects on infertility rates among couples living near the smelter in questionnaire study of 1784 females, aged 25 to 44 years. No increase of spontaneous abortion was found to be associated to smelter work or to living close to the smelter in a recently published study by Wulff et al (2002).

Blom et al (1985) performed neurophysiological studies in arsenic exposed smelter workers. The levels of arsenic were estimated to be below 500 µg/m<sup>3</sup> before 1975 and approximately 50 µg/m<sup>3</sup> thereafter. A slight risk of subclinical neuropathy was found. A slightly reduced nerve conduction velocity was more common in two of more peripheral nerves among the arsenic workers than in the referents. A statistically significant correlation between cumulative arsenic exposure and reduced nerve conduction velocity in three peripheral motor nerves was observed. In a five-year follow-up

study the adverse effects of arsenic on peripheral nerves seemed to be dependent on long-term exposure rather than on short-term fluctuations in exposure levels (Lagerkvist and Zetterlund 1994). A vasospastic tendency in the finger arteries and an increased prevalence of Raynaud's phenomenon was found by Lagerkvist et al (1986) in a study of 47 arsenic exposed smelter workers who were compared with 48 referents. The finger systolic pressure was measured at skin temperatures of 10, 15 and 30 ° C. In a follow-up study the workers were examined before and after a summer vacation of 4 to 8 weeks. After this intermission the arsenic excretion in urine decreased to normal values, while the vasospastic tendency in the finger arteries remained unchanged. Thus, the disturbances in the peripheral arteries seem to be dependent on long-term arsenic exposure and not related to short-term fluctuations in arsenic exposure (Lagerkvist et al 1988).

Low cadmium levels in blood were found in a study of mother-newborn pairs from the surroundings of a copper smelter and a control area in Northern Sweden. The most important environmental factor was shown to be smoking (Lagerkvist et al 1992). Later lead and cadmium levels were determined in blood and milk at 6 weeks after delivery in women living in the vicinity of the smelter and in a control area. In general, blood and milk concentrations were low in both areas (Hallen et al 1995). In a study of lead and calcium in blood and in the umbilical cords of 290 women living near a smelter and in 194 referents, the blood lead concentrations in the mothers increased by about 20 % and 15 %, respectively. Umbilical cord lead levels were 80 to 87 % of the maternal levels. Maternal S-calcium levels decreased during pregnancy and were significantly lower than those of the newborns. Thus, an increase in blood lead concentrations was found during pregnancy, despite increased blood volume and unchanged or decreasing environmental lead levels. The authors conclude that the mobilization of lead from the skeleton during pregnancy may explain the increase (Lagerkvist et al 1996).

## **11. AIMS OF THE THESIS**

1. To relate the mortality and cancer incidence to the cumulative lead exposure in a cohort of primary smelter workers.
2. To evaluate the lung cancer risks in primary smelter workers with concomitant exposure to lead and arsenic
3. To describe the change in lead and arsenic exposure for the exposed workers since the start of the smelter in 1930.

## **12. MATERIALS AND METHODS**

### **12.1 Study I**

This study is based on an original cohort of 3832 male workers at the Ronnskar copper and lead smelter, employed for total periods of at least three months before 1967, and followed up during the period 1950-1981. In this cohort, 1188 workers had died before January 1, 1982, the closing date of the study. The causes of death were coded according to the WHO International Classification of Diseases (8<sup>th</sup> revision). All workers were traced in the cause of death register at Statistics, Sweden. Work histories were collected from the company.

A lead cohort of 437 workers employed for at least three years at sites with considerably lead exposure 1950-1974 was extracted from the original cohort. These workers had been regularly followed by blood lead measurements since 1950.

Based on the median value (478.5 µg Pb/100 ml) of the cumulative blood lead dose 1950-1974, the lead cohort was subdivided into a high and a low exposure group (n=218, and n=219, respectively). The lead cohort was also grouped into those who at least once had exceeded B-Pb > 70 µg/ 100 ml (3.4 µmol/L; n=288) and into those who had never exceeded that level (n=149).

Two-sided statistical tests were used. Standardized mortality ratios (SMRs) and test based 95 % confidence limits were calculated (Miettinen 1976) using general reference populations.

### **12.2 Study II**

The cohort was based on 3979 primary lead smelter workers employed for at least one year during the period 1928-1979. From this original cohort, a subcohort consisting of 1992 workers were selected, who had never been employed in departments where exposure to known carcinogens such as arsenic and nickel occur or at working places such as roaster department and machine shop. Information about work-sites and employment periods at the smelter was obtained from the company. Vital status was determined on

December 31, 1987. At that date, 3523 workers were alive and 456 workers were deceased.

The expected mortality 1955 to 1987 and cancer incidence 1958-1987 were calculated relative to the county rates, specified for cause, gender, five-year age groups and calendar year. A cumulative blood lead index was formed by a summation of the annual mean blood lead values for each worker and used for dose-response analyses. SMR-values, SIR-values and 95 % confidence limits were calculated.

### **12.3 Study III**

The cohort was based on 3979 lead exposed smelter workers, employed for at least one year between 1928 and 1979, and also included in the blood lead register at the smelter that was started in 1950. Two subcohorts were formed from the original cohort. One was based on 710 workers that had been employed at the lead departments. The other consisted of workers that had been employed at the lead departments but never at other works at the smelter where an increased risk of lung cancer had been observed. The yearly cancer incidence rates for the period 1958 to 1987 were obtained from the National Swedish Tumour Registry. Standardized Cancer Incidence Rates (SIRs) were calculated and compared with county rates.

### **12.4 Study IV**

The study cohort comprised 3979 primary lead smelter workers, first employed for at least 3 months between 1928 and 1979, participating in the blood lead surveillance program that was started in 1950, and also alive at the start of follow-up in 1955. Mortality was followed from January 1, 1955 to December 31, 1987, through linkage to the Cause-of Death Register at Statistics Sweden. Similarly, the incidence of malignancies was followed from 1958 to December 31, 1987, through linkage with the national Swedish tumor register.

At the study end-point, 3523 subjects were alive and 456 were deceased. Forty-six workers (39 dead subjects and seven incident cases) had developed respiratory malignancies during the follow-up period. For each lung cancer case three aged-matched male referents, not known to have developed lung

cancer or cancer at any other site during the follow up-period (N=141) were selected from the basic cohort (N=3979). After log transformation, cases and referents were compared using conditional logistic regression with lung cancer as the outcome variable, and with smoking habits, and exposure to arsenic and inorganic lead as predictor variables.

A cumulative air arsenic exposure index was calculated (CAAEI;  $\text{mg As/m}^3 \times 10 \text{ m}^3/\text{d} \times 250 \text{ days/y} \times \text{number of exposed y}$ ) for each worker and used as the arsenic predictor variable. For lead, three different indices were calculated and used in the calculations. One was a cumulative blood lead index (CBLI = a summation of the annual mean blood lead values during the follow-up period). Another was based on the peak-blood value (PBPb), and the third on the number of years when the subject had participated in blood lead sampling during the follow-up period.

Among the cases, 72 % were smokers, 15 % nonsmokers and 13 % had unknown smoking habits. The corresponding figures for the age-matched referents were 45 %, 36 % and 19 %, respectively.

## **12.5 Measurement of exposure**

In order to document the exposure pattern during the different time periods of production at the smelter an investigation of performed measurements of air levels giving rise to exposure in different work places have been done. Data from the records of the Health and Safety Department at the smelter were collected.

## **13. RESULTS AND DISCUSSION**

### **13.1 Study I**

Significantly elevated SMRs compared to the Swedish general population were noted in the original cohort for total mortality (SMR = 115;  $p < 0.001$ ), circulatory system diseases (SMR = 120;  $p < 0.001$ ), cerebrovascular diseases (SMR = 129;  $p < 0.001$ ), ischemic heart diseases (SMR = 119;  $p < 0.001$ ), all malignant neoplasms (SMR = 114;  $p < 0.005$ ), lung cancer (SMR = 218;  $p < 0.001$ ) and stomach cancer (SMR = 143;  $p < 0.001$ ).

The lead cohort gave SMRs around or lower than 100 for these disease categories in relation to the general population of Sweden with the exception of lung cancer (SMR = 162) which, however, was not significantly elevated. No consistent dose-response pattern was observed when the lead cohort was subdivided into high-lead and low-lead exposed groups. Only marginal changes were noted when SMRs for all malignant neoplasms, lung cancer and stomach cancer in the groups under study were recalculated using a latency period of 15 years.

As the smelter started in 1930 and the blood lead measurements in 1950 some workers in the lead cohort might have had a considerably lead exposure, not registered in this study. The exposure levels during the 1930's and the 1940's were probably considerably higher than the levels measured later. The current threshold limit value of lead in air was often exceeded at the lead plant during the first years.

No excess risks of neoplasms were found in this study. The study could not confirm the relationship between renal neoplasms and lead exposure which has been observed in several animal experiments (Zollinger 1953, Boyland et al 1962, Roe et al 1965, van Esch and Kroes 1969, Zawirska and Medras 1968, Zawirska and Medras 1972).

The evaluation of a field material of this kind contains several complications: limited size of cohorts, multifactorial exposure, lack of smoking data etc. The exposure to potentially dangerous substances such as hexavalent chromium and arsenic, associated with lung cancer was considerably lower at the lead plant than at some other work-sites. On the other hand, all of these lead smelter workers had a mixed exposure also including metals and semi-metals such as antimony, cadmium, chromium, cobalt, lanthanum, selenium and zinc. Moreover, exposure to organic carcinogens, e.g. polyaromatic hydrocarbons such as benzo(a)pyrene had taken place.

## **13.2 Study II**

### **13.2.1 Mortality**

The total mortality and the mortality in circulatory diseases for the original cohort and for the subgroups are lower than would be expected (SMR-values from 0.8 to 1.0). In this study the different causes of deaths in the cohorts were compared with the population in the county of Vasterbotten. For all malignant neoplasms the mortality in the total material was significantly increased (SMR = 1.2). The mortality in respiratory cancer was almost threefold compared to the reference population (SMR = 2.8).

In the subgroup of lead exposed workers (N=1992), the mortality of all malignant tumours and tumours in the respiratory organs was similar to the risk in the original cohort both with and without adjustment for a latency period of 10 to 15 years.

In the highest exposed subgroup of lead exposed workers ( $\Sigma\text{BPb} \geq 10$   $\mu\text{mol/L}$ ), the SMR for all malignancies was slightly increased to 1.5 (95 % CI 0.8-2.4), and the SMR for lung cancer was considerably raised (SMR 4.1; 95 % CI 1.5-9.0). Applying a latency period of 10 to 15 years did only marginally affect these risk estimates.

### **13.2.2 Morbidity**

Lung cancer incidence was increased in the total cohort (SIR 2.8; 95 % CI 2.1-3.8). The lung cancer incidence was considerably higher in a cohort of workers first employed before 1950 (N=717) compared to those first employed 1950 and onwards (N=3225) (SIR 3.6; 95 % CI 2.6-5.0 vs SIR 1.3; 95 % CI 0.6-2.6).

Lead exposed workers, who had also been employed at the roasters, the arsenic or nickel plant, or at the machine shop showed lung cancer incidence data of the same magnitude as in the total cohort. When restricting the analysis to the subcohort of lead exposed workers, the lung cancer risks stayed at a similar level both with and without adjustment for a latency period of at least 15 years. Workers first employed before 1950 (N=228) had

a considerably higher lung cancer risk (SIR 3.7; 95 % CI 1.8-6.6) compared with those first employed 1950 and onwards (SIR 2.0; CI 0.6-4.6) (N=1764).

The lung cancer risk estimates were raised in both the intermediate ( $\Sigma$ BPb 2-10  $\mu$ mol/L) and the highest exposed subgroup ( $\Sigma$ BPb  $\geq$  10  $\mu$ mol/L) of lead exposed workers (SIR 4.5; 95 % CI 1.8-9.3 and SIR 5.1; 95 % CI 2.0-10.5; latency period of 15 years). No lung cancer cases were observed in the lowest lead exposed subgroup ( $\Sigma$ BPb 0-2  $\mu$ mol/L).

The two presented studies (I and II) are consistent regarding an increased mortality in lung cancer. In study II both mortality and morbidity was investigated. The risk estimates in study II were considerably higher than in study I. This can partly be explained by use of the county of Vasterbotten, where lung cancer is comparatively rare, as the reference population, while the general Swedish male population was used as a reference population in study I.

The increased lung cancer incidence found in the lead exposed subcohort in study II is considerably higher than in a published meta-analysis (Fu and Boffetta 1995) which reported a RR of 1.42 (95 % CI 1.1 – 1.9) when combining results from three studies of workers with heavy occupational exposure to lead. Whether this is due to the more specific quantification of lead exposure in our study or to an interaction with other agents will be further investigated.

In study II the lung cancer risk estimates were particularly raised in the subcohort of lead exposed workers, specifically in its medium and highest exposed subgroups. The tendency to a dose-response relationship for lung cancer observed in this subcohort is interesting and will be further investigated. Still, the increased lung cancer mortality and morbidity observed in these studies must be interpreted with caution since the number of highly exposed lung cancer cases is fairly low, especially in the lead exposed subcohort, and due to concomitant exposure also to other metals.

### **13.3 Study III**

The lung cancer incidence was raised in both lead subcohorts (Lead subcohort 1: SIR 2.4; 95 % CI 1.2-4.5; Lead subcohort 2: SIR 3.6; 95 % CI 1.2-8.3). The total cancer incidence was, however, not increased. A detailed

investigation of the working histories of the lung cancer cases was undertaken. In lead subcohort 1, 9 of 10 workers developing lung cancer had a significant arsenic exposure in parallel with the lead exposure. Similarly four of five lung cancer cases in lead subcohort 2 had a significant work-related exposure to arsenic. The increased risk ratios were sustained both with and without a latency period of 15 years.

Data about smoking habits was lacking for the studied workers. The study outcome must be interpreted with some caution because of the limited number of lung cancer cases. The findings indicate that an interaction effect between arsenic and lead may have taken place. In this multifactorial exposure situation it is, however, difficult to separate the effects of arsenic and lead on the lung epithelium. To get a better individual exposure assessment of the participating workers, a case-referent study will be a valuable complement to the previous cohort studies.

### **13.4 Study IV**

Exposure variables (median and ranges) for cases and referents with known smoking habits are presented in Table 1.

Table 1. Exposure variables (median and ranges; Mann-Whitney U-test) for lung cancer cases and referents with known smoking habits. CAAEI = Cumulative air arsenic exposure (CAAEI;  $\mu\text{g As/m}^3 \times 10 \text{ m}^3/\text{day} \times 250 \text{ days/year} \times \text{number of exposed years}$ ); CBLI = cumulative blood lead index ( $\mu\text{mol Pb/L}$ ); PBPb = peak blood lead concentrations ( $\mu\text{mol Pb/L}$ ), BPbY = number of years when blood lead samples were obtained from the participants. NS = Not significant. Modified from Lundstrom et al 2006.

Variables	Cases (n=40)	Referents (n=114)	p-values
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Exposure time	35 (8-48)	30 (2-50)	NS
CAAEI	6250 (2500-945 000)	3000 (2500-540 000)	0.026
CBLI	9.0 (0.6-55.4)	11.9 (0.3-74.1)	NS
PBPb	2.4 (0.6-5.8)	2.7 (0.3-4.8)	NS
BPbY	4.5 (1-26)	6.0 (1-33)	NS
Non-smokers	7	51	
Smokers	33	63	

The cumulative air arsenic exposure index (CAAEI) was significantly higher among cases than in referents. The other variables did not differ significantly between the study groups. CAAEI showed a positive correlation ( $r_s = 0.50$ ;  $P = 0.001$ ) with exposure time (employment time) among the cases, but was not related to any of the lead exposure indices (PBPb, BPbY, CBLI). The latter lead exposure indices were not associated with exposure time.

In logistic regression model 1, CAAEI, CBLI and smoking habits were used as predictor variables. The cases had a significantly higher smoking rate as compared with the referents (OR = 4.0; 95 % CI 1.6-10.1;  $p = 0.003$ ). Similar results were obtained if the other two lead exposure indices (PBPb, BPBY) were used in the calculations instead of CBLI.

In logistic regression model 2, the analysis was confined only to smokers (33 cases, 63 referents) with CAAEI and CBLI as dependent variables. The results showed that the arsenic exposure was significantly higher among the cases (OR = 1.07; 95 % CI 1.02 – 1.11;  $p = 0.005$ ) than in the referents. The lead exposure was, however, of the same magnitude in the two groups. Similar results were obtained if using PBPb or BPbY instead of CBLI as predictors of lead exposure.

The main finding in this study is that cumulative arsenic exposure and smoking were identified as statistically significant risk factors for the development of lung cancer. The lead exposure was, however, not identified as a statistically significant risk factor for lung cancer. The outcome was the same for the three lead exposure indices that was used as lead exposure predictors in the calculations.

Due to the low number of nonsmokers among the cases it was not possible to perform a similar regression model 2 calculation in nonsmoking cases and referents. Besides arsenic and lead, the workers have also been exposed to other metals such as e.g. copper, nickel and selenium, as well as to dusts, fumes and gases. These concomitant exposures have been difficult to quantify.

#### 14. MEASUREMENTS OF LEAD AND ARSENIC EXPOSURE

The Swedish National Institute of Public Health, Stockholm, was established in 1938. Around 1940, the Company involved the Institute in the preventive work. Dust sampling at fixed sampling stations were occasionally made since the early 1940's, and thereafter gradually extended. Occupational hygiene measurements showed air arsenic concentrations ranging from about 0.35 to 1.5 mg/m<sup>3</sup> at the roasters during the late 1940's. During the 1950's the air arsenic concentrations measured ranged between 0.1-0.5 mg/m<sup>3</sup>. The air arsenic concentrations at different plants at the Ronnskar smelter from 1950 to 2005 are presented in table 2. As evident from the table there has been a considerable decrease of the exposure during the last decades. The exposure at the arsenic plant in 1974 was about 3400 µg/m<sup>3</sup> as compared with about 25 µg/m<sup>3</sup> in the middle of the 1980's. The same pattern is shown at the copper plant. The arsenic plant was closed in 1991.

Table 2. Air arsenic measurements at the smelter 1950 - 2005. All values in mg/m<sup>3</sup>. P = personal sampling. All other values are from stationary sampling.

Year	Arsenic plant	Lead plant	Lead Kaldo	Clinker furnace	Copper plant	Roasters
1950						
1952	5.3				2.3	1.0
1953						

1954					0.08	0.9
1961					0.06	1.0
1962						
1974	3.4				0.3	0.4
1975	0.52	0.022 (P)	0.058	0.020	0.06	0.062
1985	0.024 (P) 0.022	0.002	0.021	0.024	0.052 (P)	
1995					0.005 (P) 0.007	
2005					0.005 (P) 0.015	

Air lead concentrations could exceed 1 mg/m<sup>3</sup> at the lead plant during the 1940's (Nygren 1980, Pershagen 1982). The air lead levels at different plants at the smelter from 1950 to 2005 are shown in table 3.

Table 3. Air lead measurements at the smelter 1950 - 2005. All values in mg/m<sup>3</sup>. P = personal sampling. All other values are from stationary sampling. mv = mean values.

Year	Original lead plant	Lead Kaldo	Clinker furnace	Copper plant	Roasters
1950				1.2	
1952	11.5				0.4
1953				1.2	
1954					1.0

1958	49.3				
1961				0.2	0.03
1962	3.5			0.6	
1974					1.7
1975	0.55 (P) (mv)	0.159	0.11 (mv)	0.18 (P)	0.214
1985	0.1 (P)	0.14	0.034	0.187	
1995		0.270 0.281 (P)	0.098 (P) 0.082	0.036 (P) 0.089	
2005		0.020 0.065 (P)	0.047 (P) 0.091	0.078 (P) 0.191	

Also for lead there has been a significant decrease of the air lead concentrations since the 1970's. This is particularly evident at the lead plant. The lead Kaldo plant started in 1976 and gradually took over the lead production. Accordingly, the original lead plant was closed in 1989.

## 15. GENERAL DISCUSSION

### 15.1 Main findings

In study I, the original cohort showed an increased total mortality, an increased mortality in circulatory diseases, cerebrovascular diseases, ischemic heart diseases, and in all malignant neoplasms including lung cancer and stomach cancer. In the lead subcohort, however, the corresponding SMRs were lower than or around 100 for all disease categories in relation to the general population of Sweden with the exception of lung cancer, which, however, was not significantly elevated. In study II, both the original cohort and the subcohort of lead workers showed an excess rate of deaths from lung cancer. Workers hired before 1950 showed a higher lung cancer incidence than workers employed later. The risk estimates for lung cancer were further elevated in the highest exposed subcohort of lead workers giving a SIR-value of 5.1 (95% CI 2.0-10.5; latency period of 15 years). No excesses of other malignancies were observed.

To further elucidate the possible carcinogenicity of lead the Swedish cohort (III) was further analysed by forming two subcohorts from the original

cohort of 3979 male smelter workers. One consisted of 710 workers employed at the lead departments but also at other departments at the smelter. The other one consisted of 383 workers that had been employed at the lead departments and at other departments, but never at other works where an excess of lung cancer had previously been reported. Standardized Cancer Incidence Rates (SIR) 1958-1987 were calculated relative to county rates. The lung cancer incidence was raised in both lead subcohorts (SIR 2.4; 95% CI 1.2-4.5; SIR 3.6; 95% CI 1.2-8.3), but not the total cancer incidence. A detailed study of the working histories in the 10 lung cancer cases identified, however, revealed that all but one had had a significant exposure also to arsenic.

To further analyze the possible impact from arsenic exposure a nested case-control study was undertaken (IV) including 46 lung cancer cases and 141 age-matched male referents. The main finding in this study was that cumulative arsenic exposure and smoking were identified as statistically significant risk factors for the development of lung cancer in a logistic regression model. The lead exposure, however, was not. The outcome was the same for the three lead exposure indices (cumulative blood lead; peak blood lead; number of lead exposed years) that was used as lead exposure predictors in the calculations.

## **15.2 Discussion of methods and results**

### **15.2.1 Lead exposure**

As shown in Table 3, section 14, there has been a significant decrease of the air lead concentration since the 1970's. This is particularly evident at the lead plant.

The biological monitoring of the lead exposed workers started in 1950. Blood lead samples were regularly obtained from the lead plant workers up to four to six times per year, giving a unique blood lead register. For some of the lead workers more than 300 blood lead samples have been collected

during their employment period. The sampling frequency in lead exposed workers at other metal producing plants was sparser. Emission spectrometry was used for the blood lead determinations up to 1969. Thereafter, the analyses have been performed by atomic absorption spectrophotometry. Up to the 1970's, the laboratory had a regular exchange of blood lead samples for quality control with similar laboratories in the United Kingdom and West Germany showing good agreement (Hoschek 1963, Holmqvist 1976). From 1970 and onwards, the laboratory has participated in a national quality control program coordinated by the National Board of Occupational Safety and Health in Stockholm, Sweden. The results have consistently been close to the expected concentrations.

Three blood lead indices have been used in studies II-IV: cumulative blood lead index (CBLI) = summation of annual mean blood lead values; peak blood lead values and number of years when at least one blood lead sample was obtained from the worker. The lead exposure at the lead plant was highest during the first decades. In 1950, the mean blood lead value of lead plant workers was 3.0  $\mu\text{mol/L}$ . Thereafter a gradual decrease of the lead exposure took place leading to a mean blood lead value of 1.6  $\mu\text{mol/L}$  in 1987. A similar decline was observed also among other personnel at the smelter. During the same period, the mean blood lead level decreased from 2.6 to 0.6  $\mu\text{mol/L}$  in transportation and maintenance workers, showing that lead exposure was not only confined to the lead departments. Since 1987, the gradual decrease of the blood lead concentrations among lead workers and other workers at the smelter have continued (Figure 2).

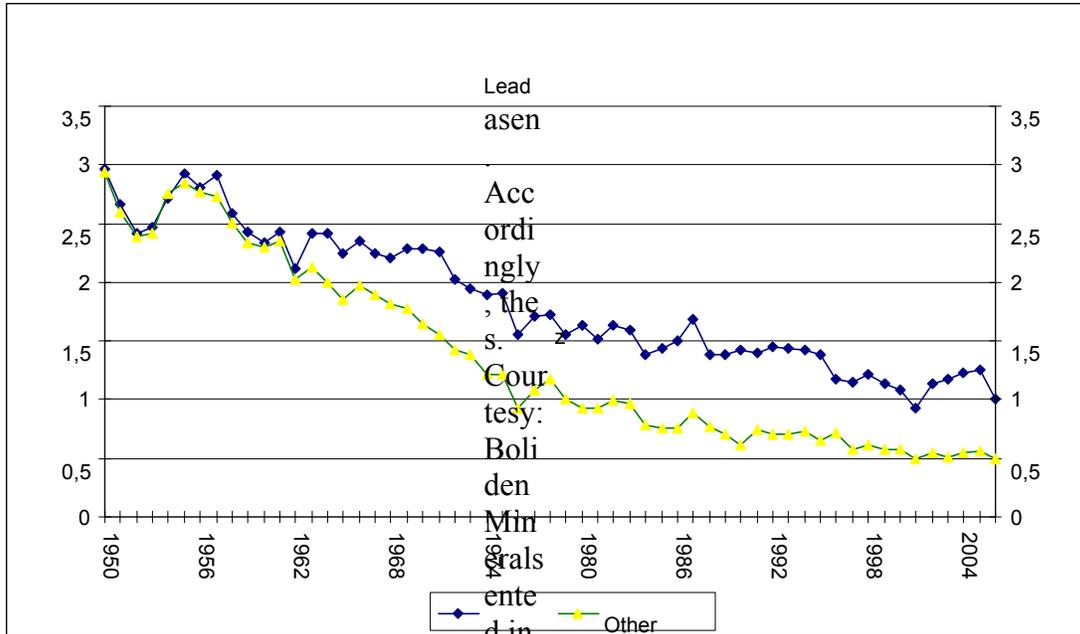


Figure 2. Mean annual blood lead concentrations ( $\mu\text{mol/L}$ ) in lead workers (upper curve) and workers at other plants (lower curve) at the smelter 1950 - 2006.

### 15.2.2 Arsenic exposure

The Swedish National Institute of Public Health, Stockholm, was established in 1938. Around 1940, the Company involved the Institute in the preventive work. Dust sampling at fixed sampling stations were occasionally made since the early 1940's, and thereafter gradually extended. Occupational hygiene measurements showed air arsenic concentrations ranging from

about 0.35 to 1.5 mg/m<sup>3</sup> at the roasters during the late 1940's. During the 1950's the air arsenic concentrations measured ranged between 0.1-0.5 mg/m<sup>3</sup>. A job-exposure matrix (JEM) constructed by Nygren (1980) was used to estimate the individual airborne arsenic exposure. He classified the exposure for airborne arsenic, dust and sulphur dioxide (SO<sub>2</sub>) for approximately 25 plants at the smelter from the 1930's and up to 1980. For most plants the exposure was subdivided into three time periods depending on measured air concentrations, the enforcement of new production technologies, medical and technical preventive measures undertaken to improve the working environment, the use of personal breathing protective devices etc. As evident from table 2, section 14, there has been a considerable decrease of the exposure during the last decades

For working periods from 1980 and up to 1987, additional arsenic exposure was calculated in cooperation with industrial hygienists at the department of occupational health at the smelter. Based on these estimates a cumulative airborne arsenic exposure index (CAA EI) was calculated during the follow-up period for all participants in study IV. The detailed investigation showed that the heaviest arsenic exposure at the smelter took place during the 1930's to 1950's. Very few of the cases and referents in study IV were arsenic-exposed during the 1980's.

### **15.2.3 Smoking**

Smoking data were lacking in the three cohort studies (I-III). Smoking is a well known risk factor for the development of lung cancer. In some studies, the smoking frequency has been higher among blue-collar workers in comparison with the general population. A previous study at the same smelter (Sandstrom and Wall 1995) showed that the prevalence of smoking had gradually decreased since the 1970's. In this study, the smoking frequencies were comparable with national figures for similar social and occupational strata. Adjustment for smoking did not alter the lung cancer gradient between employment cohorts or between job categories. In a study by Siemiatycki et al (1988) confounding from smoking would increase the lung cancer risk up to 1.2 (OR) in some occupations. Thus, it seems unlikely that confounding from smoking would explain an important part of the increased lung cancer incidence observed in studies I-III.

In the present case referent study (IV) smoking data were collected from medical records at the department of occupational health at the smelter and classified into three categories: smoker, non-smoker, unknown smoking habits. Among the lung cancer cases there were 72 % smokers, 15 % non-smokers, and 13 % with unknown smoking habits. The corresponding figures for the age-matched referents were 45 %, 36 % and 19 %, respectively. Smoking was thus an important and statistically significant risk factor for lung cancer in the present studies.

#### **15.2.4 Other exposures**

A problem with studies at a primary smelter is the multifactorial exposure to and influence from other metals, dusts, fumes and gases (Cooper et al 1985, Selevan et al 1985, Ades and Kazantzis 1988) and a potential for interactions certainly exists. Such interactions have been recently reviewed (Nordberg et al 2007). Previous studies of tissue concentrations in deceased smelter workers with lung cancer have shown the highest concentrations of antimony, arsenic, cadmium, lanthanum, and lead and the lowest selenium levels in lung tissue in comparison with workers who died of other diseases (Gerhardsson et al 1985, Gerhardsson et al 1986). The workers at this primary smelter have also been exposed to irritating gases such as sulfur dioxide and to polyaromatic hydrocarbons, e.g. benzo(a)pyrene. These concomitant exposures have been difficult to quantify.

The dominant exposure to lead and other metals at the smelter is in the form of slowly soluble oxides and sulfides. These compounds have a low solubility in water and the solubility in the mucous secretion in the lung may be of the same magnitude. These low soluble compounds can be expected to have a long biological half-time in the lung tissues.

#### **15.2.5 Validity of incidence and mortality data**

The reporting and registration of the lung cancer cases at the smelter has been similar to that of the national or county populations. Data from the national Swedish Cancer Register have been shown to have a high validity. As reported by Mattsson (1984) about 96 % of all newly diagnosed lung cancer cases are reported to the register. Thus, the cancer incidence results

presented in our studies probable have a higher validity than the mortality data.

### **15.2.6 Causes of lung cancer in smelter workers**

Inorganic lead has for a long period been a suspected human carcinogen. Different forms of lead, e.g. lead acetate, lead subacetate, and lead phosphate have caused kidney and brain tumors in rodents following oral and parenteral exposure. In 1987, IARC concluded that there was sufficient evidence in experiments on animals to classify inorganic lead as an animal carcinogen. In 2006, IARC upgraded inorganic lead as a possible human carcinogen (2A).

Increased risks of lung cancer were reported in a large US study presented in section 3.6.1; (Kang et al 1980, Cooper 1981, Cooper et al 1985, Cooper 1988, Wong and Harris 2000). Most of the subjects had a multifactorial exposure (e.g. SO<sub>2</sub>, arsenic and cadmium) and smoking data were lacking. Similar findings were reported by Rencher et al (1977) in an US study at a large western copper smelter. These workers also had a multifactorial exposure (e.g. SO<sub>2</sub>, H<sub>2</sub>SO<sub>4</sub>, As, Pb and Cu). The study at a British zinc-cadmium smelter (Ades and Kazantzis 1988) showed an increased lung cancer mortality that was related to time of employment, as well as to cumulative lead and arsenic exposure. In this study smoking data were lacking for 93-94 % of the population. Similar increases of lung cancer risks were observed in our studies I-III, where specific data on smoking and arsenic exposure were lacking.

As presented above and in section 3.6.1, the investigations of lead exposed workers show disparate findings with reported increases of lung, kidney, stomach, thyroid and endocrine system malignancies in some of the studies. No consistent pattern was seen. The increased risks for malignancies in lung, kidney and stomach are modest and may be explained by confounding factors, not accounted for. Some of the studies are hampered by small numbers, reducing the power. Basically all studies are complicated by a multifactorial exposure situation and lack of detailed data as regards individual exposure to lead as well as to other exposures in the working environment. Data about dietary and smoking habits are missing in most studies.

Ecological, case-control and cohort studies have shown a significant dose-response pattern between arsenic concentrations in drinking water and increased lung cancer risks (Tsai et al 1999, Boffetta 2004, Chen et al 2004, Navarro et al 2007) and arsenic in drinking water has been classified as a group 1 carcinogen to humans (IARC 2004). Several case-control and cohort studies in smelter workers have shown a significantly raised mortality from respiratory cancer among the exposed workers (Pinto et al 1978, Enterline and Marsh 1982, NRC 1999, IARC 2004, Jones et al 2007).

In animal studies on Syrian golden hamsters arsenic and cigarette smoke have been found to synergistically increase the DNA oxidation in the lung (Hays et al 2006). An interaction between inhaled inorganic arsenic and cigarette smoking for the development of lung cancer has been reported by Jarup and Pershagen (1991). Similar results have been observed in a study of about 10 600 residents in arseniasis-endemic areas in Taiwan. The study showed a significant dose-response trend of ingested arsenic on lung cancer risk. This trend was more prominent among cigarette smokers (Chen et al 2004). This increased risk of developing lung cancer may also appear in arsenic exposed non-smokers (Neuberger and Field 2003). A mutually enhancing effect of arsenic and smoking is thus well established for lung cancer. In our study IV such an interaction was also indicated (section 13.4). However there was no significant effect of lead exposure. Although our studies cannot exclude an effect of lead exposure on the occurrence of lung cancer, the importance of concomitant smoking and arsenic exposure for observed increases in lung cancer risks among lead smelter workers with such combined exposures has been clearly indicated in the present studies.

## **16. CONCLUSIONS**

In conclusion, cumulative arsenic exposure and smoking were identified as significant risk factors for the development of lung cancer in the studied primary smelter workers. Lead exposure, however, was not identified as a significant risk factor for lung cancer in the final analysis (IV). On the other hand, from our results it can not be excluded that inorganic lead can play a minor role in the multifactorial genesis of lung cancer, possibly through synergism with other carcinogenic exposures including arsenic and smoking.

Our studies also show that exposure for arsenic and other metals in the smelter have decreased dramatically by a factor of ten or more, since the

1970's. The risks for lung cancer at the smelter most probably have decreased accordingly.

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